CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-990

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	**21-990 N000**
Submission Dates:	2/22, 3/31, 4/11, 4/25, 6/22, 8/15, 8/22, 9/22, 10/5, 2006
Brand Name:	**Exforge**
Generic Name:	amlodipine besylate and valsartan
Dosage Form & Strength:	Combination Tablets ——— 160/5 mg; 160/10 mg; 320/5 mg; and 320/10 mg
Indication:	Hypertension
Applicant:	Novartis Pharmaceuticals Corp.
Submission:	Original NDA
Divisions:	DPEI and Cardio-Renal Drug Products, HFD-110
Primary Reviewer:	Elena V. Mishina, Ph.D.
Team Leaders:	Patrick Marroum, Ph.D.

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-990 and finds the clinical pharmacology and biopharmaceutics sections acceptable. The requested biowaivers for the 5/80mg, 5/160mg and 10/320mg dosage strength are granted.

The Agency recommends the following dissolution method and specifications for valsartan:

Apparatus:	USP II (paddle)
Medium:	0.067 M phosphate buffer, pH 6.8, 37°C
Dissolution Volume:	900 ml
Rotation Speed:	50 rpm
Specification:	Q = _____

And for amlodipine:

Apparatus	USP II (paddle)
Medium	0.1N HCL, pH 1.0, 37°C
Dissolution Volume	900 ml
Rotation Speed (rpm)	50 rpm
Specification:	Q= _____

1.2 COMMENTS:

Issue not addressed by the sponsor:
The highest recommended dose (DDI Guidance for Industry) was not evaluated in the drug-drug interaction study neither for valsartan nor for amlodipine. However, since there is no mechanistic basis for a pharmacokinetic interaction, studying higher doses of these drugs will most probably result in the same outcome.

_____ Date_____
Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

_____
Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

CPB Briefing was held on October 23, 2006

Attendees: Drs..
cc list: NDA 21-990, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

1.3 Summary of OCBP Findings

1.3.1 Background

Novartis Pharmaceuticals is seeking approval for Exforge (amlodipine besylate and valsartan) combination tablets for the treatment of hypertension. Amlodipine besylate is a calcium channel blocker approved for the treatment of hypertension (Norvasc, NDA 19-787). Valsartan is an angiotensin receptor blocker also approved for the treatment of hypertension (Diovan, NDA 21-283). This NDA is submitted as a 505(b)(2) application and contains reports of safety and effectiveness of the combination drug.

Exforge was evaluated in five controlled clinical trials involving over 5000 patients with hypertension where valsartan and amlodipine were administered as capsules (clinical service forms) and as free combinations. In order to bridge the clinical efficacy and safety data obtained with the clinical service forms as free combination to the intended fixed combination tablet products, a bioequivalence development program was designed.

1.3.2 Current Submission

Item 6 of NDA 21-990 contains 7 study reports including two bioavailability studies with prototype formulations, three definitive bioequivalence studies with the dose strengths 80/2.5 mg [Study A2303], 160/10 mg [Study A2310] and 320/5 mg [Study A2309] of valsartan/amlodipine, drug-drug interaction and food effect studies. All studies have been reviewed. There are two types of valsartan/amlodipine fixed dose formulations: monolithic tablets (80/5, 160/5 and 160/10 mg doses) and bi-layer tablets (320/5 and 320/10 mg doses).

The sponsor requested biowaivers for the following dose strengths: 80/5 mg, 160/5 mg and 320/10 mg of valsartan/amlodipine based on the tablet dissolution information. This information has been reviewed.

Pharmacokinetics

All clinical pharmacology studies submitted with this NDA were performed in healthy subjects. Pharmacokinetics of valsartan and amlodipine have been well characterized and published extensively in the literature. The individual study reports were provided in previous NDA 19-787 and NDA 21-283.

Absorption, Distribution, Metabolism, Excretion

Amlodipine

Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 80%. The bioavailability of amlodipine is not altered by the presence of food.

The apparent volume of distribution of amlodipine is 21 L. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Valsartan

Following oral administration of valsartan alone peak plasma concentrations of valsartan are reached in 2 to 4 hours. Absolute bioavailability is about 23%. Food decreases the exposure (as

measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%.
The steady state volume of distribution of valsartan after intravenous administration is 17 L indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.
Valsartan shows bi-exponential decay kinetics following intravenous administration with an average elimination half-life of about 6 hours. The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isoenzymes.
Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Exforge
Following oral administration of Exforge® (amlodipine besylate and valsartan) peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6-8 hours, respectively. The rate and extent of absorption of Exforge are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets (Table 1).

Table 1. Relative Bioavailability of Valsartan and Amlodipine

	Formulation		
Valsartan/Amlodipine, mg	80/2.5	160/10	320/5
Relative BA (Fixed/Free), %	98/105	95/101	111/101

Drug-drug interaction information
The pharmacokinetic interaction was studied between single doses of 5 mg of amlodipine and 160 mg of valsartan. The parameter values (AUC and Cmax) for both drugs were similar when administered alone or in combination except for the Cmax values of valsartan (31% decrease when coadministered with amlodipine). Since these drugs are intended for chronic administration, the difference in valsartan Cmax values is deemed to be not clinically significant.

Exposure-Response Relationships
No exposure-response relationship was established for Exforge.

Biopharmaceutics
The following dissolution method and specifications are recommended:

Valsartan

Apparatus:	USP II (paddle)
Medium:	0.067 M phosphate buffer, pH 6.8, 37°C
Dissolution Volume:	900 ml
Rotation Speed:	50 rpm
Specification:	Q = [redacted]

Amlodipine:

Apparatus	USP II (paddle)
Medium	0.1N HCL, pH 1.0, 37°C
Dissolution Volume	900 ml
Rotation Speed (rpm)	50 rpm
Specification:	Q= [redacted]

The requested biowaivers for the 5/80mg, 5/160mg and 10/320mg dosage strength are granted based on comparability of the dissolution profiles in 3 media.

2 QUESTION BASED REVIEW

2.1 General Attributes

History of Exforge Development

Exforge is a combination product of an angiotensin receptor blocker (ARB) valsartan and dihydropyridine calcium channel blocker (CCB) amlodipine besylate. The sponsor proposed this combination product for more effective lowering of blood pressure.

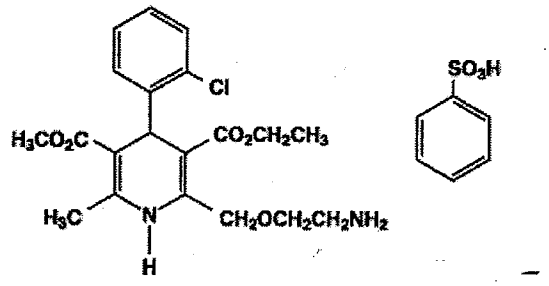
Valsartan was first developed for the treatment of hypertension and is approved for this use alone or in combination with other antihypertensive agents in once daily doses of 80 mg – 320 mg in the US and 80 mg -160 mg in other countries. It has been marketed for hypertension as monotherapy since 1996 and in combination with hydrochlorothiazide since 1997.

Amlodipine is approved for the treatment of hypertension and is available in doses of 5 and 10 mg and in some countries in a 2.5 mg dose for once daily administration.

The sponsor is seeking the approval of Exforge for the treatment of hypertension.

Highlights of chemistry and physical-chemical properties of the drug substance and product

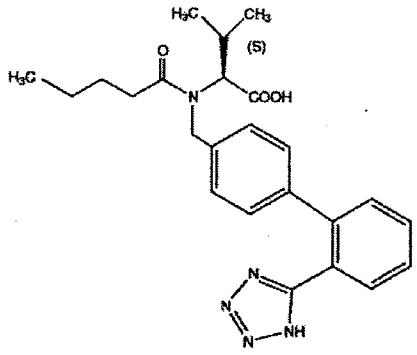
Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl-5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate; its structural formula is



Its empirical formula is C20H25CIN2O5•C6H6O3S and its molecular weight is 567.1.

Amlodipine besylate is the besylate salt of amlodipine, a dihydropyridine calcium channel blocker (CCB).

Valsartan is a white to practically white fine powder, soluble in ethanol and methanol and slightly soluble in water. Valsartan's chemical name is N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-valine; its structural formula is



Its empirical formula is C24H29N5O3 and its molecular weight is 435.5.
Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype.
Exforge® (amlodipine besylate and valsartan) is a fixed combination of amlodipine besylate and valsartan. The inactive ingredients for all strengths of the tablets are colloidal silicone dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. Additionally the 5/320 mg and 10/320 mg strengths contain iron oxide yellow and sodium starch glycolate. The film coating contains hypromellose, iron oxides, polyethylene glycol, talc and titanium dioxide.

What are the proposed mechanisms of action and therapeutic indication?

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.
Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The inhibition of the renin-angiotensin system (RAS) with ARBs may offer a more favorable tolerability profile (a reduced incidence of cough).
Both ARBs and CCBs lower blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complimentary mechanisms.

Exforge® (amlodipine besylate and valsartan) is indicated for the treatment of hypertension.

What are the proposed dosages and route of administration?

The recommended once daily dose of amlodipine besylate is -10 mg and of valsartan is mg-320 mg. The tablets are formulated in for oral administration with a combination of amlodipine equivalent to 5 mg or 10 mg of amlodipine 160 mg, or 320 mg of valsartan providing for the following available combinations: 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology section was designed to bridge the clinical efficacy and safety data obtained with clinical service forms as free combination to the intended fixed combination tablet products. The sponsor performed two bioavailability studies with prototype formulations, three definitive bioequivalence studies with the dose strengths 80/2.5 mg [Study A2303], 160/10 mg [Study A2310] and 320/5 mg [Study A2309] of valsartan/amlodipine, drug-drug interaction and food effect studies.

At the teleconference held with the sponsor on October 31, 2006, the sponsor confirmed that the formulations of amlodipine and valsartan used in the pivotal placebo-controlled clinical studies 2201 and 2307 were exactly the same as the formulations used for the definitive bioequivalence studies. For the purpose of blinding, amlodipine tablets (2.5 mg and 5 mg) in the pivotal clinical studies were overencapsulated with the addition of [redacted] (see composition Table 47, page 76). The overencapsulation of the amlodipine tablets did not change the dissolution properties of amlodipine under the tested dissolution conditions (see page 77).

There are two types of valsartan/amlodipine fixed dose formulations: monolithic tablets [redacted] 160/5 and 160/10 mg doses) and bi-layer tablets (320/5 and 320/10 mg doses). The sponsor requested biowaivers for the following dose strengths: 80/5 mg, 160/5 mg and 320/10 mg of valsartan/amlodipine based on the tablet dissolution information.

All studies were conducted utilizing healthy subjects.

Was there a reasonable basis for selecting the response endpoints and were they measured properly to assess efficacy and safety in the clinical pharmacology studies?

Efficacy and safety of the combination product Exforge were not assessed in the clinical pharmacology studies.

Were the correct moieties identified and properly measured to assess clinical pharmacology?

Yes.

The sponsor used the properly validated assay of valsartan and amlodipine in plasma. The assay validation reports were provided for each of the studies. The results provided for the assay validation were acceptable.

Were the relationship between efficacy endpoints and safety endpoints and drug plasma concentration described?

No. The sponsor did not plan to describe the exposure-response relationship for this combination drug productd.

2.3 Intrinsic Factors

What is the inter-and intra-subject variability of the PK parameters, and what are the major causes of variability?

Valsartan is a highly variable drug. Amlodipine is a moderately variable drug.

The ranges of intra-subject variability (%CV) associated with Cmax and AUC of valsartan and amlodipine from three definitive BE studies are provided in the Table 2. The causes of variability were investigated in the original NDA for amlodipine and valsartan.

Table 2. Intra-subject (%CV) in three definitive BE studies

	Valsartan			Amlodipine		
	VAA489 A2303	VAA489 A2309	VAA489 A2310	VAA489 A2303	VAA489 A2309	VAA489 A2310
Fixed Combo (Test)	46-54%	31-38%	24-30%	11–12%	10-13%	9-16%
Free Combo (Reference)	35-47%	31-38%	23-33%	9-11%	9-12%	10-11%

2.4 Extrinsic Factors

Is there an in vitro basis to suspect in vivo drug-drug interactions?

Amlodipine is a calcium channel blocker of the dihydropyridine class; valsartan is a specific competitive angiotensin II antagonist of the AT1 receptor subtype.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Valsartan is eliminated mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isoenzymes.

Since these drugs have different metabolic pathways, the pharmacokinetic interaction between them is not expected.

2.5 General Biopharmaceutics

What are the solubility characteristics of Exforge?

Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol.

Valsartan is a soluble in ethanol and methanol and slightly soluble in water.

Was an adequate link established between the clinical and to be marketed formulations of Exforge?

Yes. Three studies established the link between the clinical and to be marketed formulations of Exforge for the ——— 160/10 mg and 320/5mg tablet strength.

The final market image (FMI) tablet containing ——————— of amlodipine met the bioequivalence criteria relative to the free combination of clinical service formulations (CSF) of ——————————— capsules with respect to amlodipine (AUC and Cmax) and to valsartan (AUC) but not with respect to valsartan Cmax. Considering the wide therapeutic window and titratablility of the drug, the differences on valsartan Cmax (increase by 17%) would not be clinically significant (Table 3).

Table 3. Statistical analysis results of valsartan PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (µg/mL)	Fixed (fixed)*	1.8	1.17	1.06-1.29
	Free (reference)**	1.6		
$AUC0_{-t}$ (h*µg/mL)	Fixed (test)*	10.4	1.12	1.03-1.21
	Free (reference)**	9.3		
$AUC_{0-\infty}$ (h*ng/mL)	Fixed (test)*	10.7	1.11	1.02-1.20
	Free (reference)**	9.7		

*Fixed is the test treatment: 80/2.5 valsartan/amlodipine [redacted] combination tablet.
**Free is the reference treatment: 80/2.5 free combination of 80 valsartan CSF capsules and 2.5 mg amlodipine CSF capsule.

Table 4. Statistical analysis results of amlodipine PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (pg/mL)	Fixed (fixed)*	1443.5	0.97	0.95-1.00
	Free (reference)**	1482.9		
AUC_{0-t} (h*pg/mL)	Fixed (test)*	74637.9	1.01	0.99-1.03
	Free (reference)**	73944.8		
$AUC_{0-\infty}$ (h*pg/mL)	Fixed (test)*	82292.3	1.01	0.99-1.03
	Free (reference)**	81299.9		

*test treatment: 80/2.5 valsartan/amlodipine [redacted] combination tablet.
**reference treatment: 80/2.5 free combination of 80 valsartan CSF capsules and 2.5 mg amlodipine CSF capsule.

The FMI tablet containing 160 mg of valsartan and 10 mg of amlodipine met the bioequivalence criteria relative to the free combination of CSFs of 160 mg valsartan and 10 mg amlodipine capsules with respect to both AUC and Cmax. Summary results of valsartan and amlodipine PK parameters are shown in Table 5and Table 6.

Table 5. Summary results of valsartan PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (µg/mL)	Fixed (fixed)*	3.0	1.01	0.93-1.09
	Free (reference)**	3.0		
AUC_{0-t} (h*µg/mL)	Fixed (test)*	20.6	0.98	0.92-1.05
	Free (reference)**	20.9		
$AUC_{0-\infty}$ (h*ng/mL)	Fixed (test)*	21.1	0.98	0.92-1.05
	Free (reference)**	21.5		

*test treatment: 160/10 valsartan/amlodipine final market image (FMI) combination tablet.
**reference treatment: free combination of 160 mg valsartan CSF capsule and 10 mg amlodipine CSF (2X5 mg) capsules.

Table 6. Summary results of amlodipine PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (pg/mL)	Fixed (fixed)*	5472.6	1.03	1.01-1.06
	Free (reference)**	5292.2		
AUC_{0-t} (h*pg/mL)	Fixed (test)*	272296.3	1.05	1.02-1.07
	Free (reference)**	260375.0		
$AUC_{0-\infty}$ (h*pg/mL)	Fixed (test)*	299116.8	1.05	1.03-1.07
	Free (reference)**	284604.7		

*test treatment: 160/10 valsartan/amlodipine final market image (FMI) combination tablet.
**reference treatment: free combination of 160 mg valsartan and 10 mg amlodipine CSF capsules.

The FMI tablet containing 320 mg of valsartan and 5 mg of amlodipine met the bioequivalence criteria relative to the free combination of CSF of 320 mg valsartan and 5 mg amlodipine capsules with respect to both AUC and Cmax. Statistical analysis results of valsartan and amlodipine PK parameters are shown in Tables 7 and 8.

Table 7. Statistical analysis results of valsartan PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (µg/mL)	Fixed (fixed)*	5.2	0.91	0.85 – 0.98
	Free (reference)**	5.7		
AUC_{0-t} (h*µg/mL)	Fixed (test)*	37.9	0.95	0.90 – 1.00
	Free (reference)**	39.8		
$AUC_{0-\infty}$ (h*ng/mL)	Fixed (test)*	38.9	0.95	0.91 – 1.00
	Free (reference)**	40.8		

*test treatment: 320/5 valsartan/amlodipine final market image (FMI) combination tablet.
**reference treatment: 320/5 free combination of 160 mg valsartan and 5 mg amlodipine CSF capsules.

Table 8. Statistical Analysis Results of Amlodipine PK Parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (pg/mL)	Fixed (fixed)*	2111.7	0.99	0.97 – 1.02
	Free (reference)**	2122.7		
AUC_{0-t} (h*pg/mL)	Fixed (test)*	107274.0	0.99	0.96 – 1.02
	Free (reference)**	107966.0		
$AUC_{0-\infty}$ (h*pg/mL)	Fixed (test)*	117567.4	1.01	0.99 – 1.03
	Free (reference)**	116640.4		

*Fixed is the test treatment: 320/5 valsartan/amlodipine final market image (FMI) combination tablet.
**Free is the reference treatment: 320/5 free combination of 160 mg valsartan and 5 mg amlodipine CSF capsules.

Was a biowaiver granted for the tablet strengths which were not included in BE studies?

Yes. Since BE studies have not been performed for the 5/80mg, 5/160mg and 10/320mg film coated amlodipine besylate and valsartan tablets, a biowaiver was requested for these strengths. Comparative dissolution profiles were obtained on film-coated tablets in three different media, pH 6.8 (phosphate buffer), pH 4.5 (acetate buffer) and pH 1.0 (0.1 N HCl), 900 ml of dissolution

media were used in Apparatus II (paddle) at 50 rpm. Dissolution profiles in the 3 media are provided comparing 5/80mg to 10/160mg, 2.5/80mg to 5/160mg and 5/320mg to 10/320mg strengths. In addition, f2 similarity factors were calculated for each combination of tablets tested. The bio-waiver for each of the valsartan/amlodipine fixed combination —— tablet strength was granted based on the following:

1. The composition of 80/5 mg valsartan/amlodipine fixed combination —— tablet is proportional in its active and inactive ingredients to the 160/10 mg valsartan/amlodipine fixed combination —— tablet, for which the bioequivalence was established. The quantitative composition of the clinical formulations for Exforge tablets is shown in the Table 45 (Appendix) on a mg per tablet and % w/w basis.
2. The manufacturing process of the two products is identical.
3. Valsartan and amlodipine exhibit linear and dose proportional pharmacokinetics.
4. In vitro dissolution profiles of valsartan and amlodipine are similar in three pH media between each of the valsartan/amlodipine fixed combination —— tablet strength as evidenced by the results of the f2 test.

Was there an impact of food on the bioavailability of Exforge?

The sponsor performed a food effect study. Following a single dose oral administration of 160/10 mg valsartan/amlodipine fixed combination tablet, the mean AUC values of valsartan were similar in the fed and fasting conditions and the mean Cmax values decreased by 16% in fed compared to fasting condition. The mean Cmax and AUC of amlodipine were similar between fed and fasting conditions. Valsartan/amlodipine fixed dose combination tablets (Exforge) can be administered without regards to meals.

Are the dissolution specifications acceptable?

The dissolution method and specifications proposed by the sponsor are not acceptable.
The sponsor sent additional information for the justification for the use of a phosphate buffer medium at pH 6.8 for both drugs with 0.1% Tween 80 at rotation speed of 65 rpm.

1. The sponsor reported that the amlodipine solubility is not significantly different from pH 1 to 6.8, therefore, the use of pH 6.8 for both drugs was proposed.

The information submitted for the biowaivers had amlodipine dissolution profiles at pH from 1.0 to 6.8 (Figure 14, Figure 15, Figure 16, Figure 20, Figure 21, Figure 22, Figure 26, Figure 27, Figure 28 in the Appendix). Apparently, the solubility of amlodipine depends on the pH of the medium. For example, the release of amlodipine at 30 minutes from the valsartan/amlodipine tablet of 320/10 mg was —— (pH 6.8) —— (pH 4.5) and —— (pH 1).

2. The sponsor proposed to add 0.1% Tween 80 to the dissolution media to decrease the adsorption of amlodipine to glass and metal surfaces during the dissolution process to decrease the variability of the method.

The raw data show the opposite: when Tween was used, the variabilities of the tablet dissolution were larger than without Tween (Table 52 in the Appendix).

3. The sponsor proposed to increase the dissolution rate of amlodipine by the use of 65 rpm rotation speed.

The three rotation speeds (50, 65 and 75 rpm) are compared in (Table 54 and Table 55, Appendix). The dissolution of amlodipine at 65 rpm speed was higher than at 50 rpm. The sponsor did not provide the comparison of different rotation speeds with and without Tween 80. When the 65 rpm rotation speed was used, the variability of the method was very high. Since the dissolution methods and specifications used for the biowaiver provide satisfactory results, the Agency used these results to recommend using two different dissolution methods for valsartan and amlodipine (the same dissolution method used for the monoentities).

Valsartan:

Apparatus:	USP II (paddle)
Medium:	0.067 M phosphate buffer, pH 6.8, 37°C
Dissolution Volume:	900 ml
Rotation Speed:	50 rpm
Specification:	Q = ———

Amlodipine:

Apparatus	USP II (paddle)
Medium	0.1N HCL, pH 1.0, 37°C
Dissolution Volume	900 ml
Rotation Speed (rpm)	50 rpm
Specification:	Q= ———

2.6 Analytical section

How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In an earlier clinical pharmacology study [CP-Protocol 37], valsartan was analyzed in plasma using an HPLC method with fluorescence detection. The LLOQ of valsartan with this method was 50 ng/mL. In the biopharmaceutics studies pertaining to this submission, valsartan was analyzed in plasma using a specific LC-MS/MS method with an LLOQ of 20 ng/mL using 0.1 mL plasma. Both assays were fully validated, and within study validation data are provided in each of the study reports.

In the study [CP-Protocol 37], amlodipine in plasma was determined by using a capillary gas chromatography (GC) method. The LLOQ of amlodipine with this method was 0.18 ng/mL. In the pilot bioavailability studies, amlodipine in plasma was analyzed using a modified specific LC-MS/MS method (Yasuda T, Tanaka M, Iba K (1996) with an LLOQ of 0.075 ng/mL using 1 mL plasma. In the definitive bioequivalence studies, amlodipine in plasma was analyzed using specific LC-MS/MS methods with an LLOQ of 0.0248 ng/mL using a range of 0.1-0.5 mL plasma.

Were the validation characteristics of the assay acceptable?

Yes.
Both assays have their validation reports, see individual study reviews.

What is the overall conclusion regarding NDA 21-990?

Overall the Clinical Pharmacology and Biopharmaceutics section is acceptable.

4.2 Individual Study Reviews

4.2.1 An open-label, randomized, single dose, three period, crossover pilot study to determine the relative bioavailability of 160/10 mg and 80/2.5 mg prototype fixed combination valsartan/amlodipine tablets to a free combination of marketed 160 mg valsartan and 10 mg amlodipine tablets

Study No. [VAA489A2302]
Name of finished product: Diovan® and amlodipine
Name of active ingredient (s): valsartan and amlodipine
Investigator(s): [redacted]
Study period: first subject dosed 25-Oct-2003 last subject completed 29-Nov-2003

Objectives:
Primary
• To determine the bioavailability of 160/10 and 80/2.5 mg fixed combination valsartan/amlodipine tablets relative to a free combination of 160 mg valsartan and 10 mg amlodipine tablets.
Secondary
• To assess the safety and tolerability of a fixed combination of 160/10 and 80/2.5 mg of valsartan/amlodipine tablets.

Design:
This study employed an open-label, randomized, single dose, three-period, crossover design. A total of 27 healthy male and female subjects were enrolled for at least 24 to complete all study treatments and procedures. Each subject participated in a screening period, three baseline periods, three treatment periods, washout period of at least fourteen days between each treatment, and a study completion evaluation. Subjects were randomized to complete each of the following treatments under fasting conditions:
Treatment A: Single dose of 160/10 mg fixed combination valsartan/amlodipine tablet
Treatment B: Single dose of 80/2.5 mg fixed combination valsartan/amlodipine tablet
Treatment C: Single dose of free combination of 160 mg valsartan and 10 mg amlodipine tablets

In each treatment period, subjects were admitted to the study site and remained domiciled for at least 48 hours after dosing for pharmacokinetic assessment. Study completion evaluation was performed following the 168-hour blood draw of the last treatment period or in the case of early termination prior to discharge from the study site.

Number of subjects: 27 subjects were dosed, 25 subjects completed the study.

Criteria for inclusion: Healthy, non-smoking male and female subjects between 18 and 45 years of age and in good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests and urinalysis.

Investigational drug:

• 160/10 mg fixed combination valsartan/amlodipine tablet (Package Control #03-0557US, KN#6001267.002, Batch#AEUS/2003-0205)
• 80/2.5 mg fixed combination valsartan/amlodipine tablet (Package Control #03-0557US; KN#6001266.003, Batch# AEUS/2003-0206)

Comparator drugs:
The following two drugs were given in combination
• 160 mg valsartan tablet (Diovan®) (Lot# 569H1015)
• 10 mg amlodipine tablet (Norvasc®) (Lot# 3QL188A)

Duration of treatment:
Single oral dose in each treatment period, with at least a fourteen-day washout period between each dosing

Criteria for evaluation:
Safety and tolerability: Monitoring and recording of all adverse events beginning after the first dose, pre-dose and end-of-study monitoring of hematology, blood chemistry and urine parameters, occasional monitoring of vital signs during treatment periods and performance of physical examinations and ECGs.

Pharmacokinetics: Plasma levels of Valsartan (LC/MS/MS detection; LOQ 20 ng/mL using 100 µL of plasma), amlodipine (LC/MS/MS detection; LOQ 0.075 ng/mL using 1 mL of plasma) were determined each period at the following timepoints:
• Valsartan: Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose
• Amlodipine: Predose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 144 and 168 hours post dose
The PK parameters AUC0-t, AUC0-8, Cmax, tmax, and t½ for both Valsartan and Amlodipine were calculated, using non-compartmental methods. Descriptive statistics of all calculated PK parameters were determined. Values for Valsartan and Amlodipine were compared for the free combination (reference) and fixed combination (test formulation) dosing.

Statistical methods: Log-transformed AUC and Cmax were analyzed by a linear mixed effect model, with fixed effects from sequence, treatment and period and random effects from subject nested in with sequence. The resulting 90% confidence intervals of the appropriate treatment mean ratios were used to evaluate relative bioavailability between the fixed combination (test formulation) and the free combination (reference formulation).

Results: This study was completed as scheduled. At completion, 27 subjects had been randomized, 25 subjects had completed all study procedures and 2 subjects had discontinued (5120 subject discontinued due to an AE and subject 5123 due to an abnormal laboratory value).

Assay: Determination of valsartan in plasma by an automated 96-well solid-phase extraction procedure and analysis of the extract by liquid chromatography /tandem mass spectrometry (HPLC-MS/MS) using turbo ion spray (TIS) positive ion mode. Chromatograms were shown.

Table 9. Assay Characteristics for Valsartan

Parameter	Measure	Reviewer Comment
Linearity	0.02mcg/mL to 10mcg/mL	Satisfactory
Precision (CV %)	≤ 6.2%	Satisfactory
Accuracy Between day	between -5.3% and 7.8%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory

Bioanalytical method for determination of amlodipine: liquid-liquid extraction of plasma samples followed by evaporation of the extracts to dryness and analysis of the reconstituted samples by HPLC-MS/MS using atmospheric pressure chemical ionization.

Table 10: Assay Characteristics for Amlodipine

Parameter	Measure	Reviewer Comment
Linearity	0.075ng/mL to 15ng/mL	Satisfactory
Precision (CV %)	≤ 7.7%	Satisfactory
Accuracy Between day	between -0.7% and 0.7%	Satisfactory
LLOQ	0.075ng/mL	Satisfactory
Specificity		Satisfactory

Pharmacokinetics:

Valsartan: The summary of Pharmacokinetic parameters of valsartan after a single dose administration of the fixed combinations of 160/10 and 80/2.5 mg of valsartan/amlodipine and a free combination of 160 mg valsartan and 10 mg amlodipine are given below.

Table 11. PK Parameters of Valsartan

PK parameter*	160/10 mg Fixed Combo	80/2.5 mg Fixed Combo	160 + 10 mg Free combo
$AUC_{0-\infty}$ (µg.h/ml)	34.5 ± 13.4 (38.9%)	16.7 ± 7.6 (45.6%)	34.7 ± 15.6 (44.9%)
AUC_{0-t} (µg.h/ml)	33.6 ± 13.6 (40.5%)	16.3 ± 7.7 (47%)	34.3 ± 15.5 (45.4%)
Cmax (µg.h/ml)	4.6 ± 2.0 (42.7%)	2.4 ± 1.2 (50.3%)	4.7 ± 2.0 (43.3%)
Tmax (h)**	3 (1 – 6)	3 (1 – 6)	3 (2 – 6)
$T_{1/2}$ (h)	10.5 ± 5.2! (49.9%)	7.6 ± 4.6 (61.4%)	8.2 ± 3.2 (38.6%)

*PK parameters are expressed as arithmetic mean ± SD [CV%]; ** median (range); ! t1/2 value (90.9 hrs)of Subject 5105 was not included in the calculation.

Amlodipine: The summary of Pharmacokinetic parameters of amlodipine after a single dose administration of the fixed combinations of 160/10 and 80/2.5 mg of valsartan/amlodipine and a free combination of 160 mg valsartan and 10 mg amlodipine.

Table 12. PK Parameters of Amlodipine

PK parameter*	160/10 mg Fixed Combo	80/2.5 mg Fixed Combo	160 + 10 mg Free Combo
$AUC_{0-\infty}$ (ng.h/ml)	282.8 ± 90.1 (31.9%)	64.5 ± 20.3 (31.5%)	298.1 ± 103.8 (34.8%)
AUC_{0-t} (ng.h/ml)	265.9 ± 79.5 (29.9%)	57.9 ± 19.2 (33.2%)	281.7 ± 94.8 (33.7%)
Cmax (ng.h/ml)	6.0 ± 1.7 (27.6%)	1.4 ± 0.4 (30.9%)	6.3 ± 2.4 (38.9%)
Tmax (h)**	10 (3 – 12)	10 (8 – 24)	10 (6 – 12)
$T_{1/2}$ (h)	39.5 ± 7.9 (20%)	38.7 ± 9.3 (24.1%)	39.3 ± 7.5 (19.1%)

*PK parameters are expressed as arithmetic mean ± SD [CV%]; ** median (range)

Statistics: The summary analysis results for pharmacokinetic parameters of valsartan and amlodipine (all completed subjects with evaluable parameters on both treatments)

Table 13. Statistical Evaluations

Valsartan/ Amlodipine	Analyte	Pharmacokinetic Parameter	Treatment	Geometric mean (N)	Ratio of geometric means (test/reference)**	90% CI for ratio ***
160/10 mg Fixed Combination	Valsartan	AUC_{0-t}	Test Reference	30.2 30.5	0.99	(0.84, 1.17)
		C_{max}	Test Reference	4.1 4.2	0.97	(0.77, 1.21)
	Amlodipine	AUC_{0-t}	Test Reference	256.3 272.7	0.94	(0.87, 1.02)
		C_{max}	Test Reference	5.8 6.0	0.97	(0.88, 1.06)
80/2.5 mg Fixed Combination$	Valsartan	AUC_{0-t}	Test Reference	29.0 30.5	0.95	(0.81, 1.12)
		C_{max}	Test Reference	4.0 4.2	0.96	(0.77, 1.20)
	Amlodipine	AUC_{0-t}	Test Reference	219.5 272.7	0.80	(0.74, 0.87)
		C_{max}	Test Reference	5.3 6.0	0.88	(0.80, 0.97)

N: number of observations (N = 25-27) $ Statistical evaluations were performed on dose adjusted PK parameters ** The ratio of means on the original scale is estimated by the antilog of the difference in least square means on the log scale; reference treatment = free combination of 160 mg valsartan + 10 mg amlodipine *** The confidence interval for the ratio of means on the original scale is obtained by taking the anti-logs of the confidence limits for the difference of the treatment least square means on the log scale

Sponsor's Conclusions:

- Bioavailabilities of both valsartan and amlodipine from the 160/10 mg fixed combination tablet are similar to the free combination.
- Dose adjusted bioavailability of valsartan from the 80/2.5 mg fixed combination tablet is comparable to the free combination.
- Dose adjusted AUC0-t of amlodipine from 80/2.5 mg fixed combination tablet is about 20% less compared to the free combination, while Cmax is similar.

16 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

3 DETAILED LABELING RECOMMENDATIONS

GENERAL

The Agency considered that the information provided in the original NDA 21-990 valsartan and amlodipine combination tablets was appropriate.

CLINICAL PHARMACOLOGY COMMENTS

Labeling Comments:

CLINICAL PHARMACOLOGY Section should be read as follows:

4.2.2 An open-label, randomized, single dose, three period, crossover pilot study to determine the relative bioavailability of two 320/5 mg prototype fixed combination valsartan/amlodipine tablets to a free combination of marketed 320 mg valsartan and 5 mg amlodipine tablets.

Study No: VAA489A2311
Name of finished product: Diovan® and amlodipine
Name of active ingredient: valsartan and amlodipine
Investigator(s): [redacted]
Dates: first subject dosed 25-Oct-03 last subject completed 03-Dec-03

Objectives:
Primary
• To determine the bioavailability of two prototype fixed combination tablets of 320/5 mg valsartan/amlodipine relative to a free combination of 320 mg valsartan and 5 mg amlodipine tablets.
Secondary
• To assess the safety and tolerability of two prototype fixed combination tablets of 320/5 mg valsartan/amlodipine.

Design: This study employed an open-label, randomized, single dose, three-period, crossover design. A total of 27 healthy male and female subjects were enrolled for at least 24 to complete all study treatments and procedures. Each subject participated in a screening period, three baseline periods, three treatment periods, washout period of at least fourteen days between each treatment period, and a study completion evaluation. Subjects were randomized to complete each of the following treatments under fasting conditions:

Treatment A:
Single dose of 320/5 mg fixed combination valsartan/amlodipine tablet (prototype I)
Treatment B:
Single dose of 320/5 mg fixed combination valsartan/amlodipine tablet (prototype II)
Treatment C:
Single dose of free combination of 320 mg valsartan and 5 mg amlodipine tablets

In each treatment period, subjects were admitted to the study site and remained domiciled for at least 48 hours after dosing for pharmacokinetic assessment. Study completion evaluation was performed following the 168-hour blood draw of the last treatment period or in the case of early termination prior to discharge from the study site.

Number of subjects: 27 subjects were dosed, 24 subjects completed the study Criteria for inclusion: Healthy, non-smoking male and female subjects between 18 and 45 years of age and in good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests and urinalysis

Investigational drugs:

• 320/5 mg fixed combination valsartan/amlodipine tablet, Prototype I (Package Control #03-0558US; KN# 6001265.003 and Batch # AEUS/2003-0215)
• 320/5 mg fixed combination valsartan/amlodipine tablet, Prototype II (Package Control #03-0558US; KN# 6001265.004 and Batch # AEUS/2003-0240)

Comparator drugs:
The following two drugs were given in combination
• 320 mg valsartan tablet (Diovan®) (Lot# 054H0305)
• 5 mg amlodipine tablet (Norvasc®) (Lot# 3QL037E)

Duration of treatment: Single oral dose in each treatment period, with at least a fourteen-day washout period between each dosing

Criteria for evaluation:
Pharmacokinetics: Plasma levels of Valsartan (LC/MS/MS detection; LOQ 20 ng/mL using 100 µL of plasma), amlodipine (LC/MS/MS detection; LOQ 0.075 ng/mL using 1 mL of plasma) were determined each period at the following timepoints:
Valsartan: Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose
Amlodipine: Predose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 144 and 168 hours post dose
The PK parameters AUC0-t, AUC0-8, Cmax, tmax, and t½ for both Valsartan and Amlodipine were calculated, using non-compartmental methods. Descriptive statistics of all calculated PK parameters were determined. Values for Valsartan and Amlodipine were compared for the free combination (reference) and fixed combination (test formulation) dosing.

Statistical methods: Log-transformed AUC and Cmax were analyzed by a linear mixed effects model, with fixed effects from sequence, treatment and period and a random effect from subject nested within sequence. The resulting 90% confidence intervals of the appropriate treatment mean ratios were used to evaluate relative bioavailability between the fixed combination (test formulation) and the free (reference formulation).

Results:
Assay: Determination of valsartan in plasma by an automated 96-well solid-phase extraction procedure and analysis of the extract by liquid chromatography /tandem mass spectrometry (HPLC-MS/MS) using turbo ion spray (TIS) positive ion mode. Chromatograms were shown.

Table 14: Assay Characteristics for Valsartan

Parameter	Measure	Reviewer Comment
Linearity	0.02mcg/mL to 10mcg/mL	Satisfactory
Precision (CV %)	≤ 5.8%	Satisfactory
Accuracy Between day	between -3.8% and 7.2%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory

Bioanalytical method for determination of amlodipine: liquid-liquid extraction of plasma samples followed by evaporation of the extracts to dryness and analysis of the reconstituted samples by HPLC-MS/MS using atmospheric pressure chemical ionization.

Table 15: Assay Characteristics for Amlodipine

Parameter	Measure	Reviewer Comment
Linearity	0.075ng/mL to 15ng/mL	Satisfactory
Precision (CV %)	≤ 4.3%	Satisfactory
Accuracy Between day	between -1.3% and 1.9%	Satisfactory
LLOQ	0.075ng/mL	Satisfactory
Specificity		Satisfactory

Pharmacokinetics: Valsartan: The summary of pharmacokinetic parameters of valsartan after a single dose administration of two prototype fixed combination tablets of 320/5 mg of valsartan/amlodipine and a free combination of 320 mg valsartan and 5 mg amlodipine is given below.

Table 16. Pharmacokinetic Parameters Of Valsartan

PK parameter*	320/5 mg Fixed Combo (Prototype I)	320/5 mg Fixed Combo (Prototype II)	320+5 mg free combination
$AUC_{0-\infty}$ (µg.h/ml)	51.8 ± 29.8 (57.5%)	50.8 ± 17.8 (35%)	58.0 ± 27.1 (46.8%)
AUC_{0-t} (µg.h/ml)	50.9 ± 29.8 (58.5%)	49.6 ± 17.4 (35.1%)	57.1 ± 26.7 (46.8%)
Cmax (µg.h/ml)	6.6 ± 3.4 (52.3%)	6.4 ± 1.9 (29.4%)	7.3 ± 2.9 (39.2%)
Tmax (h)**	3 (1 – 6)	3 (1 – 6)	3 (1 – 4)
$T_{1/2}$ (h)	8.7 ± 2.7 (30.8%)	10.0 ± 5.5 (54.6%)	9.2 ± 4.0 (43.4%)

*PK parameters are expressed as arithmetic mean ± SD [CV%]; ** median (range)

Amlodipine:
The summary of the pharmacokinetic parameters of amlodipine after a single dose administration two prototype fixed combinations of 320/5 mg of valsartan/amlodipine and a free combination of 320 mg valsartan and 5 mg amlodipine is given below.

Table 17. Pharmacokinetic Parameters Of Amlodipine

PK parameter*	320/5 mg Fixed Combo (Prototype I)	320/5 mg Fixed Combo (Prototype II)	320+5 mg free combination (Reference)
$AUC_{0-\infty}$ (ng.h/ml)	127.6 ± 41.0 (32.2%)	125.5 ± 41.0 (32.7%)	127.3 ± 46.8 (36.7%)
AUC_{0-t} (ng.h/ml)	114.6 ± 36.3 (31.6%)	115.9 ± 37.4 (32.3%)	117.4 ± 43.1 (36.7%)
Cmax (ng.h/ml)	2.5 ± 0.7 (29.3%)	2.4 ± 0.6 (24.7%)	2.5 ± 0.8 (31.2%)
Tmax (h)**	10 (0.5 – 12)	10 (8.0 – 12)	10 (6 – 12)
T1/2 (h)	44.0 ± 14.1 (32.1%)	41.5 ± 9.4 (22.7%)	42.2 ± 8.9 (21.1%)

* PK parameters are expressed as arithmetic mean ± SD [CV%]; ** median (range)

Statistics: The summary analysis results for pharmacokinetic parameters of valsartan and amlodipine (all completed subjects with evaluable parameters on both treatments) are as follows

Table 18. Statistics Analysis Results

Valsartan/ Amlodipine	Analyte	Pharmacokinetic Parameter	Treatment	Geometric mean (N*)	Ratio of geometric means (test/reference)**	90% CI for ratio ***
320/5 mg Fixed Combination (Prototype I)	Valsartan	AUC_{0-t}	Test Reference	43.1 51.6	0.83	(0.71, 0.99)
		C_{max}	Test Reference	5.4 6.9	0.79	(0.63, 0.98)
	Amlodipine	AUC_{0-t}	Test Reference	109.3 109.9	0.99	(0.93, 1.06)
		C_{max}	Test Reference	2.4 2.4	1.01	(0.94, 1.09)
320/5 mg Fixed Combination (Prototype II)	Valsartan	AUC_{0-t}	Test Reference	46.3 51.6	0.90	(0.76, 1.06)
		C_{max}	Test Reference	6.1 6.9	0.88	(0.71, 1.10)
	Amlodipine	AUC_{0-t}	Test Reference	109.2 109.9	0.99	(0.93, 1.06)
		C_{max}	Test Reference	2.4 2.4	0.99	(0.92, 1.07)

Sponsor's Conclusions:

• Bioavailability of valsartan from two prototype fixed combination tablets of 320/5 mg is 10-21% less compared to that of free combination. Of the two fixed combination variants, prototype II is more comparable to the free combination than prototype I.

• Bioavailability of amlodipine from two prototype fixed combination tablets of 320/5 mg is comparable to the free combination.

• Single administrations of the fixed combination tablets (320/5 mg valsartan/amlodipine) were safe and well tolerated in healthy volunteers.

4.2.3 An open-label, randomized, single-dose, crossover, replicate study to demonstrate the bioequivalency between the fixed combination of 80/2.5 mg valsartan/amlodipine [redacted] tablet and the free combination of clinical service formulations (CSF) of 80 mg valsartan and 2.5 mg amlodipine

Study No. [VAA489A2303]
Name of finished product: VAA489 [redacted]
Name of active ingredient: valsartan and amlodipine fixed combination
Investigator(s): [redacted]
Study center(s): [redacted]
Study period First patient enrolled: 15-Mar-2005 Last patient completed: 10-Aug-2005
Phase of development: Phase III

Objectives:
Primary
• To demonstrate the bioequivalence of a fixed combination of 80/2.5 mg of valsartan/amlodipine [redacted] tablet relative to a free combination of 80 mg valsartan (CSF) and 2.5 mg amlodipine (CSF).
Secondary
• To assess the safety and tolerability of a fixed combination of 80/2.5 mg of valsartan/amlodipine tablet.

Design: This study was designed as an open-label, randomized, single-dose, four-period, replicate, crossover study. A total of 68 healthy male and female subjects were enrolled. Each subject participated in a 21-day screening period, four baseline and treatment periods and an end-of study evaluation. An inter dose interval of at least 14 days was allowed between doses. During the four treatment periods the following two treatments were given twice under fasting conditions:
• Treatment A: Single dose of 80/2.5 mg fixed combination valsartan/amlodipine [redacted] tablet [Investigational]
• Treatment B: Single dose of free combination of 80 mg valsartan (80 mg CSF) and 2.5 mg amlodipine (2.5 mg CSF) [Comparator]

Subjects were randomized to one of the two treatment sequences: ABAB or BABA. In each treatment period, subjects were admitted to the study site at least 12 hours prior to dosing and remained domiciled for at least 48 hours after dosing for pharmacokinetic assessments. They returned to the clinic for PK blood sampling at 72, 96, 144 and 168 hours post-dose. A 14-day inter-dose interval was required between each treatment period. Study completion evaluations were to be performed following the 168-hour pharmacokinetic blood draw of the last treatment period or, in the case of early termination, prior to discharge from the study site.

Number of patients: Sixty four subjects were planned to be enrolled to yield 56 completed subjects. Seventy seven subjects were enrolled and 61 subjects completed all 4 periods in the study. Additionally, 11subjects completed at least 2 sequential periods (AB or BA) in the study.

treatment interaction. The resulting 90% confidence intervals of the treatment mean ratios were used to evaluate the bioequivalence of the fixed combination (test) formulation and the free (reference) formulation. All subjects who completed at least two periods of the study and had data for both treatments were included in the pharmacokinetic data analysis. A total of 61 subjects completed all four (4) periods and 11 subjects completed at least 2 periods (AB or BA)

Results
Demographics

Table 19. Demographic Characteristics

Number of subjects randomized		77
Age (years)	Mean	33.2
	SD	7.98
	Median	34
	Range	18 - 45
Gender – n (%)	Male	31 (40.3 %)
	Female	46 (59.7 %)
Race – n (%)	Caucasian	2 (2.6%)
	Black	9 (11.7%)
	Other	66 (85.7%)
Weight (kg)	Mean	73.23
	SD	12.42
	Median	71.4
	Range	47.3 – 110.9
Height (cm)	Mean	165.5
	SD	9.60
	Median	165.0
	Range	147 - 193
Body frame – n (%)		
	Small	10 (13.0%)
	Medium	19 (24.7)
	Large	48 (62.3)
Elbow Breadth (cm)	Mean	6.83
	SD	0.81
	Median	7.0
	Range	3.3 – 8.3

Assay: Determination of valsartan in plasma by an automated 96-well solid-phase extraction procedure and analysis of the extract by liquid chromatography /tandem mass spectrometry (HPLC-MS/MS) using turbo ion spray (TIS) positive ion mode. Chromatograms were shown.

Table 20: Assay Characteristics for Valsartan

Parameter	Measure	Reviewer Comment
Linearity	0.02mcg/mL to 10mcg/mL	Satisfactory
Precision (CV %)	$\leq$ 4.4%	Satisfactory
Accuracy Between day	between -3.3% and 2.6%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory

Bioanalytical method for determination of amlodipine: liquid-liquid extraction of plasma samples followed by evaporation of the extracts to dryness and analysis of the reconstituted samples by HPLC-MS/MS using atmospheric pressure chemical ionization.

Table 21: Assay Characteristics for Amlodipine

Parameter	Measure	Reviewer Comment
Linearity	24.8 pg/mL to 2480 pg/mL	Satisfactory
Precision (CV %)	≤ 5.1%	Satisfactory
Accuracy Between day	between -5.7% and 2.8%	Satisfactory
LLOQ	24.8 pg/mL using 0.250 mL of human lithium heparinized plasma	Satisfactory
Specificity		Satisfactory

Pharmacokinetics:

• The extent of absorption (AUC) of valsartan is equivalent, while the mean Cmax is higher by 17%, for the 80/2.5 mg valsartan/amlodipine fixed combination tablet as compared to the corresponding doses of valsartan and amlodipine administered as free combination. The 17% increase in Cmax is not considered clinically relevant.

• The rate (Cmax) and extent (AUC) of absorption of amlodipine are equivalent between the 80/2.5 mg valsartan/amlodipine fixed combination tablet and the corresponding doses of CSFs of valsartan and amlodipine administered as free combination. The summary of pharmacokinetic parameters of valsartan following the fixed and free combination of 80 mg valsartan and 2.5mg amlodipine are given below.

Table 22. PK Parameters of Valsartan

Parameter	Arithmetic mean ± SD* (CV%)	
	Fixed combination (test) (Total Obs N= 141)	Free combination (reference) (Total Obs N= 141)
t_{max} (h)**	3.00 (1.00 – 6.00)	3.00 (1.00 – 6.00)
C_{max} (µg/mL)	2.17 ± 1.17 (54.6%)	1.78 ± 0.94 (53.1%)
AUC_{0-t} (h*µg/mL)	12.31 ± 7.24 (58.8%)	10.58 ± 5.65 (53.3%)
$t_{½}$ (h)	6.98 ± 7.39 (106%)	7.65 ± 10.62 (139%)
$AUC_{0-\infty}$ (h*µg/mL)	12.64 ± 7.27 (57.5%)	10.98 ± 5.63 (51.3%)

*: The summary of PK parameters from all the subjects who had quantifiable plasma concentration versus time profiles. The statistical analysis for the 90%CI estimation was done according to the protocol (see the section on statistical results for more information). **: Median (Range)

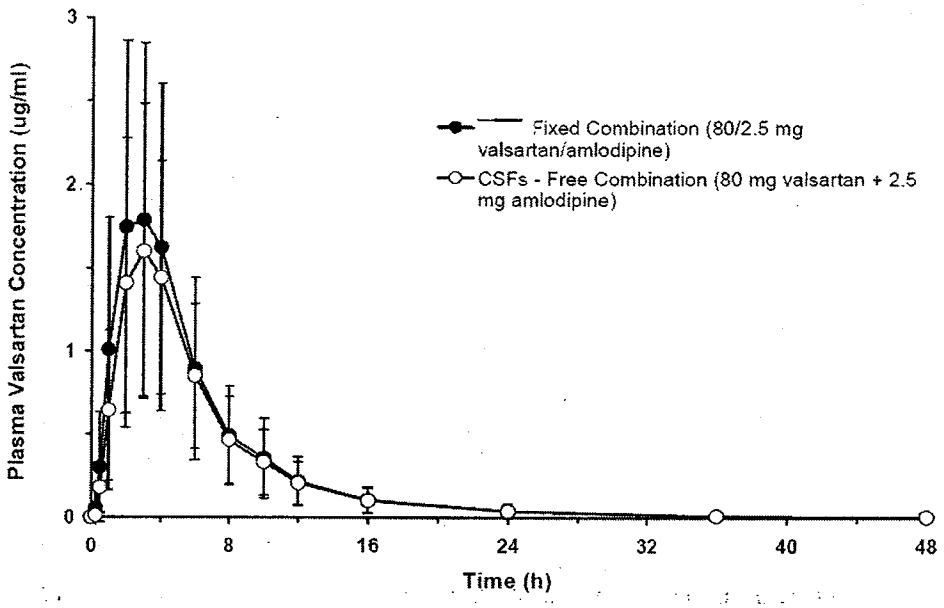


Figure 1 Mean (SD) plasma concentration-time profiles of valsartan in healthy healthy subjects following a single dose of 80 mg valsartan and 2.5 mg amlodipine as a fixed or a free combination (pooled data of replicate treatments)

The summary of pharmacokinetic parameters of amlodipine following fixed and free combination of 80 mg valsartan and 2.5mg amlodipine are given below.

Table 23. PK Parameters of Amlodipine

Parameter	Arithmetic mean ± SD* (CV%)	
	Fixed combination (test) (Total Obs N= 141)	Free combination (reference) (Total Obs N= 141)
t_{max} (h)**	8.00 (4.00 – 16.00)	8.00 (4.00 – 12.00)
C_{max} (pg/mL)	1479 ± 340 (23%)	1509 ± 343 (31%)
AUC_{0-t} (h*pg/mL)	77514 ± 23026 (30%)	76566 ± 23435 (31%)
$t_{½}$ (h)	47 ± 12 (25%)	47 ± 12 (25%)
$AUC_{0-\infty}$ (h*pg/mL)	86481 ± 27529 (32%)	85519 ± 28064 (33%)

*: The summary of PK parameters from all the subjects who had quantifiable plasma concentration versus time profiles. The statistical analysis for the 90%CI estimation was done according to the protocol (see the section on statistical results for more information). **:Median (Range) for tmax

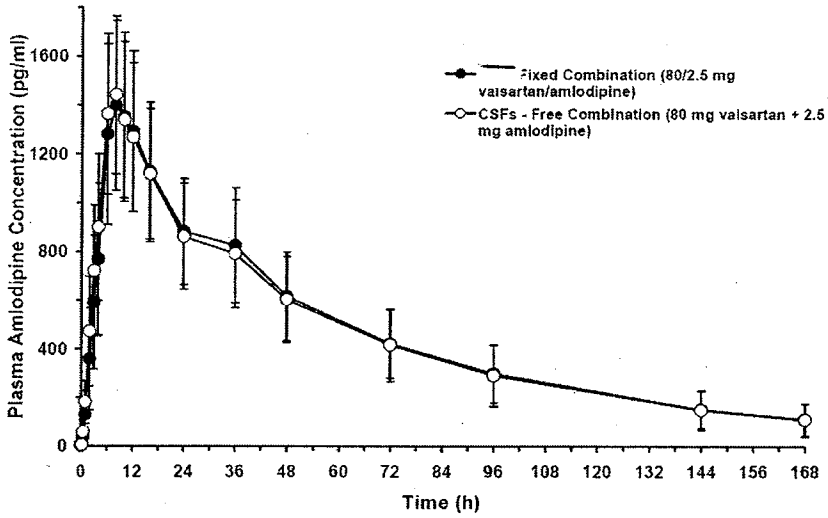


Figure 2. Mean (SD) plasma concentration-time profiles of amlodipine in healthy subjects following a single dose of 80 mg valsartan and 2.5 mg amlodipine as a fixed or a free combination (pooled data of replicate treatments)

Statistical analysis results of valsartan PK parameters are given below.

Table 24. Statistical analysis results of valsartan PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (µg/mL)	Fixed (fixed)*	1.8	1.17	1.06-1.29
	Free (reference)**	1.6		
$AUC0_{-t}$ (h*µg/mL)	Fixed (test)*	10.4	1.12	1.03-1.21
	Free (reference)**	9.3		
$AUC_{0-\infty}$ (h*ng/mL)	Fixed (test)*	10.7	1.11	1.02-1.20
	Free (reference)**	9.7		

*Fixed is the test treatment: 80/2.5 valsartan/amlodipine [redacted]ombination tablet.
**Free is the reference treatment: 80/2.5 free combination of 80 valsartan CSF capsules and 2.5 mg amlodipine CSF capsule.

Statistical analysis results of amlodipine PK parameters are given below.

Table 25. Statistical analysis results of amlodipine PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (pg/mL)	Fixed (fixed)*	1443.5	0.97	0.95-1.00
	Free (reference)**	1482.9		
AUC_{0-t} (h*pg/mL)	Fixed (test)*	74637.9	1.01	0.99-1.03
	Free (reference)**	73944.8		
$AUC_{0-\infty}$ (h*pg/mL)	Fixed (test)*	82292.3	1.01	0.99-1.03
	Free (reference)**	81299.9		

*Fixed is the test treatment: 80/2.5 valsartan/amlodipine ——— combination tablet. **Free is the reference treatment: 80/2.5 free combination of 80 valsartan CSF capsules and 2.5 mg amlodipine CSF capsule.

Sponsor's Conclusion:

• Except for the Cmax of valsartan, the — tablet containing 80 mg of valsartan and 2.5 mg of amlodipine met the bioequivalence criteria relative to the free combination of CSFs of 80 mg valsartan and 2.5 mg amlodipine capsules.

• The clinical data obtained with the free combination of 80 mg of valsartan CSF and 2.5 mg of amlodipine CSF could be extrapolated to the 80/2.5 mg valsartan/amlodipine fixed combination — tablet.

COMMENT:

1. The — tablet containing 80 mg of valsartan and 2.5 mg of amlodipine met the bioequivalence criteria relative to the free combination of CSFs of 80 mg valsartan and 2.5 mg amlodipine capsules with respect to amlodipine (AUC and Cmax) and to valsartan (AUC) but not with respect to valsartan Cmax.
2. Considering the, wide therapeutic window of the drug product and the fact that this is a titratable drug, the differences on valsartan Cmax (increase by 17%) would not be clinically significant.

4.2.4 An open-label, randomized, single-dose, crossover, replicate study to demonstrate the bioequivalency between the fixed combination of 160/10 mg valsartan/amlodipine final market image (FMI) tablet and the free combination of clinical service formulations (CSF) of 160 mg valsartan and 10 mg amlodipine

Study No. [VAA489A2309]
Name of finished product: VAA489A
Name of active ingredient: Valsartan and amlodipine fixed combination
Investigator(s): [redacted]
Study center(s): [redacted]
Study period: First patient enrolled: 15-Mar-2005 Last patient completed: 30-Sep-2005
Phase of development: Phase III

Objectives:
Primary
• To demonstrate the bioequivalence of a fixed combination of 160/10 mg of valsartan/amlodipine final market image tablet relative to a free combination of 160 mg valsartan (CSF) and 10 mg amlodipine (CSF).
Secondary
• To assess the safety and tolerability of a fixed combination of 160/10 mg of valsartan/amlodipine tablet.

Design:
This study was designed as an open-label, randomized, single-dose, four-period, replicate, crossover study. A total of 68 healthy male and female subjects were enrolled. Each subject participated in a 21-day screening period, four baseline and treatment periods and an end-of study evaluation. An inter dose interval of at least 14 days was allowed between doses. During the four treatment periods the following two treatments were given twice under fasting conditions:
• Treatment A: Single dose of 160/10 mg fixed combination valsartan/amlodipine FMI tablet [Investigational]
• Treatment B: Single dose of free combination of 160 mg valsartan (1 x 160 mg CSF) and 10 mg amlodipine (2 x 5 mg CSF) [Comparator]

Subjects were randomized to receive one of the two treatment sequences: ABAB or BABA. In each treatment period, subjects were admitted to the study site at least 12 hours prior to dosing and remained domiciled for at least 48 hours after dosing for pharmacokinetic assessments. The subjects returned to the clinic for PK blood sampling at 72, 96, 144 and 168 hours post-dose. A 14-day inter-dose interval was required between each treatment period. Study completion evaluations were performed following the 168-hour pharmacokinetic blood draw of the last treatment period or, in the case of early termination, prior to discharge from the study site.

Number of patients (planned and analyzed):
Sixty four subjects were planned to be enrolled to yield 56 completed subjects. Sixty eight subjects were enrolled and 54 subjects completed all 4 periods in the study. Additionally, 5 subjects completed at least 2 sequential periods (AB or BA) in the study.

Diagnosis and main criteria for inclusion:
Healthy, non-smoking male and female subjects between 18 and 45 years of age (inclusive) and in good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests and urinalysis were included in the study. Female subjects of childbearing potential were required to use or agree to use double-barrier local contraception, i.e. intra-uterine device plus condom, or spermicidal gel plus condom. In addition, all subjects were required to provide written informed consent prior to participation in the study.

Test product, dose and mode of administration, batch number:
160/10 mg fixed combination valsartan/amlodipine tablet (FMI) was supplied by Novartis. Lot number: H061KA. Batch size: ———

Reference therapy, dose and mode of administration, batch number:
- 160 mg valsartan tablet – 1 x 160 mg CSF (capsule; Novartis supplied) Lot number: X293 1103
- 10 mg amlodipine – 2 x 5 mg capsules CSF (Novartis supplied) Lot number: 09030.01

Duration of treatment: Four single dose treatment periods were separated by a minimum 14-day inter-dose interval (washout period).

Pharmacokinetics:
Blood collection:
Valsartan: (2 ml blood sample per time point into lithium heparin tubes (plasma)) Predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post dose
Amlodipine: (3 ml blood sample per time point into lithium heparin tubes (plasma)) Predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 144 and 168 hours post dose
For each time point from predose to 48-hour postdose, a single 5 ml blood sample was drawn in to lithium heparin tube (plasma) with subsequent aliquoting of the plasma into separate tubes for valsartan and amlodipine. For each time point from 72 to 168 hours postdose, a single 3 ml blood sample was drawn for amlodipine analysis.

Analytes, media and methods:
Valsartan and amlodipine in plasma was determined by two different LC-MS-MS methods. The lower limit of quantitation (LLOQ) of valsartan was 20 ng/mL using 100 µL plasma; and the LLOQ of amlodipine was 0.075 ng/mL using 0.5 mL plasma.

PK parameters:
Plasma concentration vs. time-profiles were used to determine AUC 0-t, AUC0-8, Cmax, tmax, and t½, in all subjects for both valsartan and amlodipine, using non-compartmental methods.

PK evaluations:
Descriptive statistics of all calculated PK parameters are provided. The PK parameters of valsartan and amlodipine were compared between the free combination (reference) and fixed combination (test formulation).

Statistical methods:

Log-transformed AUC and Cmax were analyzed by a linear mixed effects model, with fixed effects for sequence, treatment, and period, and random effect for subject by treatment interaction. The resulting 90% confidence intervals of the treatment mean ratios were used to evaluate the bioequivalence of the fixed combination (test) formulation and the free (reference) formulation. All subjects who completed at least two periods of the study and had data for both treatments were included in the pharmacokinetic data analysis. A total of 54 subjects completed all four (4) periods and 61 subjects had PK data from at least 2 periods (AB or BA)

Results:

Demographics:

Number of subjects randomized		68
Age (years)	Mean	30.1
	SD	7.34
	Median	29
	Range	18-45
Gender – n (%)	Male	44 (64.7%)
	Female	24 (35.3%)
Race – n (%)	Caucasian	15 (22.1%)
	Black	47 (69.1%)
	Other	6 (8.8%)
Weight (kg)	Mean	76.41
	SD	11.98
	Median	76.8
	Range	51.8-101.4
Height (cm)	Mean	173.4
	SD	9.95
	Median	172.5
	Range	150-196
Body frame – n (%)	Small	22 (32.4%)
	Medium	44 (64.7%)
	Large	2 (2.9%)
Elbow Breadth (cm)	Mean	6.69
	SD	0.62
	Median	6.8
	Range	5.1-7.8

Assay: Determination of valsartan in plasma by an automated 96-well solid-phase extraction procedure and analysis of the extract by liquid chromatography /tandem mass spectrometry (HPLC-MS/MS) using turbo ion spray (TIS) positive ion mode. Chromatograms were shown.

Table 26: Assay Characteristics for Valsartan

Parameter	Measure	Reviewer Comment
Linearity	0.02mcg/mL to 10mcg/mL	Satisfactory
Precision (CV %)	$\leq$ 5.4%	Satisfactory
Accuracy Between day	between -0.8% and 0.6%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory

Bioanalytical method for determination of amlodipine: liquid-liquid extraction of plasma samples followed by evaporation of the extracts to dryness and analysis of the reconstituted samples by HPLC-MS/MS using atmospheric pressure chemical ionization.

Table 27: Assay Characteristics for Amlodipine

Parameter	Measure	Reviewer Comment
Linearity	24.8 pg/mL to 9920 pg/mL	Satisfactory
Precision (CV %)	$\leq$ 7.7%	Satisfactory
Accuracy Between day	between -0.5% and 0.8%	Satisfactory
LLOQ	24.8 pg/mL using 0.500 mL of human plasma	Satisfactory
Specificity		Satisfactory

Pharmacokinetics:

The summary of pharmacokinetic parameters of valsartan following fixed and free combination of 160 mg valsartan and 10 mg amlodipine are given below.

Table 28. Pharmacokinetic Parameters of Valsartan

Parameter	Arithmetic mean ± SD* (CV%)	
	Fixed combination (test) (Total Obs N= 116)	Free combination (reference) (Total Obs N= 121)
t_{max} (h)**	3.04 (1.00 – 10.03)	3.00 (1.00 – 6.00)
C_{max} (µg/mL)	3.42 ± 1.50 (43.7%)	3.3 ± 1.5 (45.6%)
AUC_{0-t} (h*µg/mL)	23.13 ± 9.96 (43.1%)	23.21 ± 11.9 (51.3%)
$t_{½}$ (h)	9.10 ± 3.7 (40.6%)	9.5 ± 4.8 (50.2%)
$AUC_{0-\infty}$ (h*µg/mL)	23.61 ± 10.09 (42.7%)	23.9 ± 11.79 (49.3%)

*: The summary of PK parameters from all the subjects who had quantifiable plasma concentration versus time profiles. The statistical analysis for the 90%CI estimation was done according to the protocol (see the section on statistical results for more information). **: Median (Range)

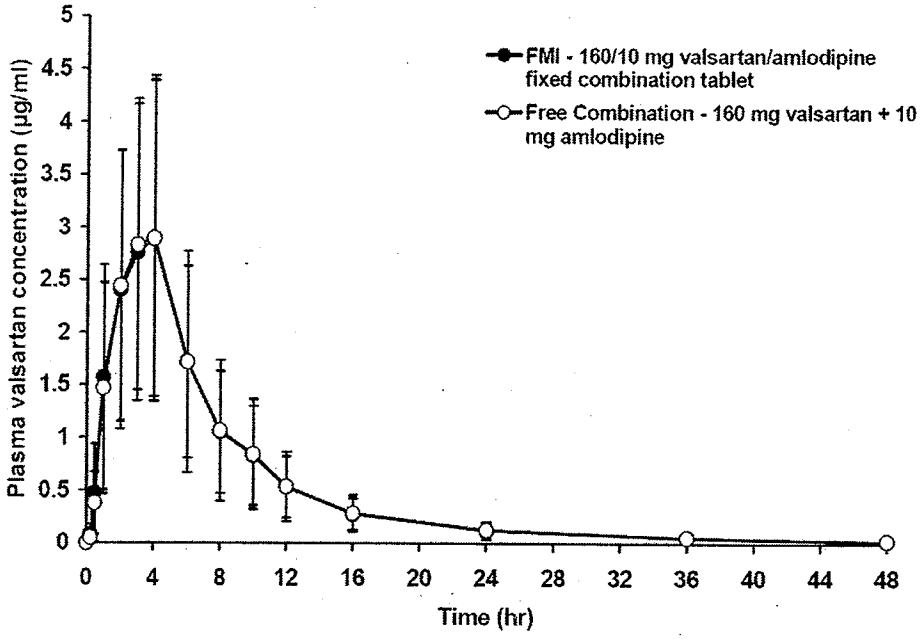


Figure 3. Mean (SD) plasma concentration-time profiles of valsartan in healthy subjects following a single dose of 160 mg valsartan and 10 mg amlodipine as a fixed or a free combination (pooled data of replicate)

The summary of pharmacokinetic parameters of amlodipine fixed and free combination of 160 mg valsartan and 10 mg amlodipine are given below.

Table 29. Pharmacokinetic Parameters of Amlodipine

Parameter	Arithmetic mean ± SD* (CV%)	
	Fixed combination (test) (Total Obs N= 117)	Free combination (reference) (Total Obs N= 121)
t_{max} (h)**	6.00 (3.00 – 96.00)	6.00 (1.00 – 16.00)
C_{max} (pg/mL)	5515 ± 1391 (25.2%)	5271 ± 1242 (23.6%)
AUC_{0-t} (h*pg/mL)	277936 ± 75043 (27%)	260416 ± 78288 (30%)
$t_{½}$ (h)	44.3 ± 8.6 (19.4%)	42.9 ± 10.2 (23.7%)
$AUC_{0-\infty}$ (h*pg/mL)	306010 ± 86996 (28%)	288210 ± 84853 (29%)

*: The summary of PK parameters from all the subjects who had quantifiable plasma concentration versus time profiles. The statistical analysis for the 90%CI estimation was done according to the protocol. **:Median (Range) for tmax

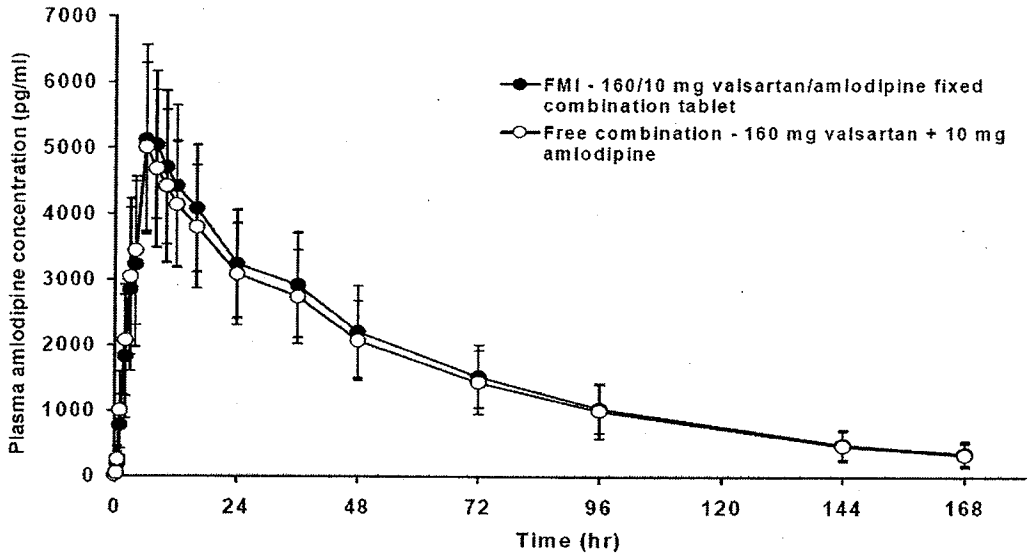


Figure 4. Mean (SD) plasma concentration-time profiles of amlodipine in healthy subjects following a single dose of 160 mg valsartan and 10 mg amlodipine as a fixed or a free combination (pooled data of replicate treatments)

The 90% confidence intervals for the ratio of geometric means (fixed/free formulations) of valsartan Cmax and AUC were completely contained in the range of (0.80, 1.25) required for claiming bioequivalence.

Summary results of the valsartan PK parameters

Table 30. Summary results of valsartan PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (µg/mL)	Fixed (fixed)*	3.0	1.01	0.93-1.09
	Free (reference)**	3.0		
AUC_{0-t} (h*µg/mL)	Fixed (test)*	20.6	0.98	0.92-1.05
	Free (reference)**	20.9		
$AUC_{0-\infty}$ (h*ng/mL)	Fixed (test)*	21.1	0.98	0.92-1.05
	Free (reference)**	21.5		

*Fixed is the test treatment: 160/10 valsartan/amlodipine final market image (FMI) combination tablet.
**Free is the reference treatment: free combination of 160 mg valsartan CSF capsule and 10 mg amlodipine CSF (2X5 mg) capsules.

The 90% confidence intervals for the ratio of geometric means (fixed/free formulations) for amlodipine Cmax and AUC were also completely contained in the range of (0.80, 1.25) required for claiming bioequivalence.
Summary results of the amlodipine PK parameters are shown below.

Table 31. Summary results of amlodipine PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (pg/mL)	Fixed (fixed)*	5472.6	1.03	1.01-1.06
	Free (reference)**	5292.2		
AUC_{0-t} (h*pg/mL)	Fixed (test)*	272296.3	1.05	1.02-1.07
	Free (reference)**	260375.0		
$AUC_{0-\infty}$ (h*pg/mL)	Fixed (test)*	299116.8	1.05	1.03-1.07
	Free (reference)**	284604.7		

*Fixed is the test treatment: 160/10 valsartan/amlodipine final market image (FMI) combination tablet. **Free is the reference treatment: free combination of 160 mg valsartan CSF capsule and 10 mg amlodipine CSF CSF (2X5 mg) capsules.

COMMENT:

The 160/10 mg of valsartan / amlodipine combination tablet is bioequivalent to the free combination of 160 mg valsartan and 10 mg amlodipine capsules coadministered together, with respect to both AUC and Cmax.

4.2.5 An open-label, randomized, single-dose, crossover, replicate study to demonstrate the bioequivalency between the fixed combination of 320/5 mg valsartan/amlodipine final market image (FMI) tablet and the free combination of clinical service formulations (CSF) of 320 mg valsartan and 5 mg amlodipine

Study No. [VAA489A2310]
Name of finished product: VAA489 (FMI)
Name of active ingredient: valsartan and amlodipine fixed combination
Investigator(s): [redacted]
Study center(s): [redacted]
Study period First patient doses: 2-Apr-05 Last patient completed: 3-Jun-2005
Phase of development: Phase III

Objectives:
Primary
• To demonstrate the bioequivalence of a fixed combination of 320/5 mg of valsartan/amlodipine final market image tablet relative to a free combination of 320 mg valsartan (2 x 160 mg CSF) and 5 mg amlodipine (CSF).
Secondary
• To assess the safety and tolerability of a fixed combination of 320/5 mg of valsartan/amlodipine tablet. The study was completed as planned.

Design:
This study was designed as an open-label, randomized, single-dose, four-period, replicate, crossover study. A total of 64 healthy male and female subjects were enrolled. Each subject participated in a 21-day screening period, four baseline and treatment periods and an end-of study evaluation. An inter dose interval of at least 14 days was allowed between doses. During the four treatment periods the following two treatments were given twice under fasting conditions:
• Treatment A: Single dose of 320/5 mg fixed combination valsartan/amlodipine FMI tablet [Investigational]
• Treatment B: Single dose of free combination of 320 mg valsartan (2 x 160 mg CSF) and 5 mg amlodipine (CSF) [Comparator]

Subjects were randomized to receive one of the two treatment sequences: ABAB or BABA. In each treatment period, subjects were admitted to the study site at least 12 hours prior to dosing and remained domiciled for at least 48 hours after dosing for pharmacokinetic assessments. They returned to the clinic for PK blood sampling at 72, 96, 144 and 168 hours post-dose. A 14-day inter-dose interval was required between each treatment period. Study completion evaluations were to be performed following the 168-hour pharmacokinetic blood draw of the last treatment period or, in the case of early termination, prior to discharge from the study site.

Number of patients : Sixty four subjects were planned to be enrolled to yield 56 completed subjects. Sixty-four (64) subjects were enrolled and fifty-three (53) subjects completed all 4 periods in the study.

Diagnosis and main criteria for inclusion: Healthy, non-smoking male and female subjects between 18 and 45 years of age (inclusive) and in good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests and urinalysis were included in the study. Female subjects of childbearing potential were required to use or agree to use double-barrier local contraception, i.e. intra-uterine device plus condom, or spermicidal gel plus condom. In addition, all subjects were required to provide written informed consent prior to participation in the study.

Test product, dose and mode of administration, batch number:
320/5 mg fixed combination valsartan/amlodipine tablet (FMI) was supplied by Novartis, Batch #: H074BA. ————————

Reference therapy, dose and mode of administration, batch number:
- 320 mg valsartan – 160 mg CSF (capsule; Novartis supplied), Batch number: X293 1103
- 5 mg amlodipine – 5 mg capsules CSF (Novartis supplied), Batch number: 09030.01

Duration of treatment: Four single dose treatment periods were separated by a minimum 14-day inter-dose interval (washout period).

Pharmacokinetics:
Blood collection:
- Valsartan: (2 ml blood sample per time point into lithium heparin tubes (plasma)) Predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post dose
- Amlodipine: (3 ml blood sample per time point into lithium heparin tubes (plasma)) Predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 144 and 168 hours post dose

For each time point from predose to 48-hour postdose, a single 5 ml blood sample was drawn in to lithium heparin tube (plasma) with subsequent aliquoting of the plasma into separate tubes for valsartan and amlodipine. For each time point from 72 to 168 hours postdose, a single 3 ml blood sample was drawn for amlodipine analysis.

Analytes, media and methods:
Valsartan and amlodipine in plasma was determined by two different LC-MS-MS methods. The lower limit of quantitation (LLOQ) of valsartan was 20 ng/mL using 100 µL plasma; and the LLOQ of amlodipine was 0.075 ng/mL using 0.5 mL plasma.

PK parameters:
Plasma concentration vs. time-profiles were used to determine AUC 0-t, AUC0-8, Cmax, tmax, and t½, in all subjects for both Valsartan and amlodipine, using non-compartmental methods.

PK evaluations:
Descriptive statistics of all calculated PK parameters are provided. The PK parameters of valsartan and amlodipine were compared between the free combination (reference) and fixed combination (test formulation).

Statistical methods: Log-transformed AUC and Cmax were analyzed by a linear mixed effects model, with fixed effects for sequence, treatment, and period, and random effects for subject by treatment interaction. The resulting 90% confidence intervals of the appropriate treatment mean

ratios were used to evaluate the bioequivalence of the fixed combination (test) formulation and the free (reference) formulation. All subjects who completed at least two periods of the study and had data for both treatments were included in the pharmacokinetic data analysis. A total of 53 subjects completed all four (4) periods and 59 subjects had data from at least 2 periods (AB or BA).

Results:

Demographics

Number of subjects randomized		64
Age (years)	Mean	32.5
	SD	7.61
	Median	33
	Range	18-45
Gender – n (%)	Male	44 (68.8%)
	Female	20 (31.3%)
Race – n (%)	Caucasian	27 (42.2%)
	Black	25(39.1%)
	Other	12 (18.7%)
Weight (kg)	Mean	79.95
	SD	14.662
	Median	80.8
	Range	51.3-108.6
Height (cm)	Mean	173.7
	SD	9.05
	Median	174
	Range	157-200
Body frame – n (%)	Small	8 (12.5%)
	Medium	27 (42.2%)
	Large	28 (43.8%)
	Not stated	1 (1.6%)
Elbow Breadth (cm)	Mean	7.23
	SD	1.034
	Median	7.3
	Range	4.1-9.8

Assay: Determination of valsartan in plasma by an automated 96-well solid-phase extraction procedure and analysis of the extract by liquid chromatography /tandem mass spectrometry (HPLC-MS/MS) using turbo ion spray (TIS) positive ion mode. Chromatograms were shown.

Table 32: Assay Characteristics for Valsartan

Parameter	Measure	Reviewer Comment
Linearity	0.02mcg/mL to 10mcg/mL	Satisfactory
Precision (CV %)	$\leq$ 4.0%	Satisfactory
Accuracy Between day	between -1.4% and 1.3%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory

Bioanalytical method for determination of amlodipine: liquid-liquid extraction of plasma samples followed by evaporation of the extracts to dryness and analysis of the reconstituted samples by HPLC-MS/MS using atmospheric pressure chemical ionization.

Table 33: Assay Characteristics for Amlodipine

Parameter	Measure	Reviewer Comment
Linearity	24.8 pg/mL to 4960 pg/mL	Satisfactory
Precision (CV %)	≤ 6.8%	Satisfactory
Accuracy Between day	between -0.7% and 1.6%	Satisfactory
LLOQ	24.8 pg/mL using 0.100 mL of human plasma	Satisfactory
Specificity		Satisfactory

Pharmacokinetics: The summary of pharmacokinetic parameters of valsartan following fixed and free combination of 320 mg valsartan and 5mg amlodipine are given below.

Table 34. Summary of Pharmacokinetic Parameters of Valsartan

Parameter	Arithmetic mean ± SD* (CV%)	
	Fixed combination (test)	Free combination (reference)
	(Total Obs N= 116)	(Total Obs N= 118)
t_{max} (h)**	3.00 (1.00 – 10.00)	3.00 (1.00 – 6.00)
C_{max} (µg/mL)	5.72 ± 2.53 (44.2%)	6.2 ± 2.62 (42.2%)
AUC_{0-t} (h*µg/mL)	40.74 ± 16.8 (41.2%)	42.62 ± 17.58 (41.2%)
$t_{½}$ (h)	9.35 ± 4.53 (48.5%)	10.16 ± 5.63 (55.4%)
$AUC_{0-\infty}$ (h*µg/mL)	41.68 ± 16.77 (40.2%)	43.65 ± 17.69 (40.5%)

*: The summary of PK parameters from all the subjects who had quantifiable plasma concentration versus time profiles. The statistical analysis for the 90%CI estimation was done according to the protocol (see the section on statistical results for more information). **: Median (Range)

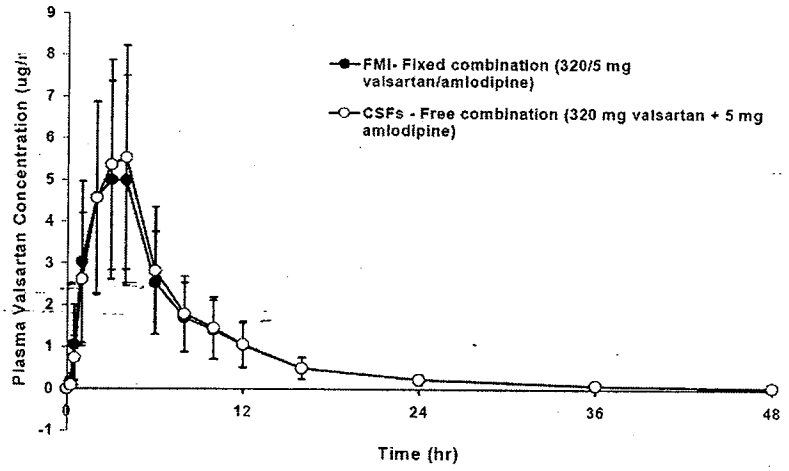


Figure 5. Mean (SD) plasma concentration-time profiles of valsartan in healthy subjects following a single dose of 320 mg valsartan and 5 mg amlodipine as a fixed or a free combination (pooled data of replicate treatments)

The summary of pharmacokinetic parameters of amlodipine fixed and free combination of 320 mg valsartan and 5mg amlodipine are given below.

Table 35. Summary Of Pharmacokinetic Parameters Of Amlodipine

Parameter	Arithmetic mean ± SD* (CV%)	
	Fixed combination (test) (Total Obs N= 116)	Free combination (reference) (Total Obs N= 118)
t_{max} (h)**	8.00 (6.00 – 49.00)	8.00 (6.00 – 16.00)
C_{max} (pg/mL)	2180 ± 581 (27%)	2187 ± 545 (25%)
AUC_{0-t} (h*pg/mL)	111883 ± 29231 (26%)	111087 ± 27798 (25%)
$t_{½}$ (h)	44 ± 13 (31%)	43 ± 11 (25%)
$AUC_{0-\infty}$ (h*pg/mL)	122599 ± 33202 (27%)	120742 ± 33584 (28%)

*: The summary of PK parameters from all the subjects who had quantifiable plasma concentration versus time profiles. **:Median (Range) for tmax

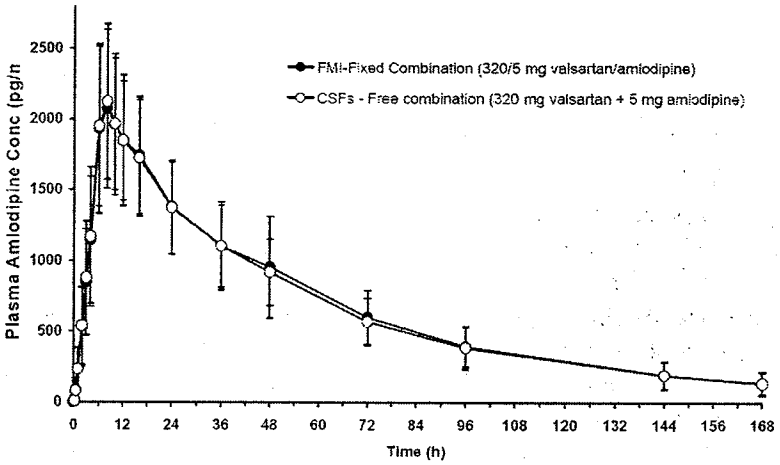


Figure 6. Mean (SD) plasma concentration-time profiles of amlodipine in healthy subjects following a single dose of 320 mg valsartan and 5 mg amlodipine as a fixed or a free combination (pooled data of replicate treatments)

Statistical analysis results of the valsartan PK parameters

Table 36. Statistical analysis results of valsartan PK parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (µg/mL)	Fixed (fixed)*	5.2	0.91	0.85 – 0.98
	Free (reference)**	5.7		
AUC_{0-t} (h*µg/mL)	Fixed (test)*	37.9	0.95	0.90 – 1.00
	Free (reference)**	39.8		
$AUC_{0-\infty}$ (h*ng/mL)	Fixed (test)*	38.9	0.95	0.91 – 1.00
	Free (reference)**	40.8		

*Fixed is the test treatment: 320/5 valsartan/amlodipine final market image (FMI) combination tablet. **Free is the reference treatment: 320/5 free combination of 160 mg valsartan CSF capsules and 5 mg amlodipine CSF capsule.

Statistical analysis results of the amlodipine PK parameters

Table 37. Statistical Analysis Results Of Amlodipine PK Parameters

Parameter	Treatment (Formulation)	Geometric mean	Ratio of geometric means Fixed/Free	90% CI for ratio
C_{max} (pg/mL)	Fixed (fixed)*	2111.7	0.99	0.97 – 1.02
	Free (reference)**	2122.7		
AUC_{0-t} (h*pg/mL)	Fixed (test)*	107274.0	0.99	0.96 – 1.02
	Free (reference)**	107966.0		
$AUC_{0-\infty}$ (h*pg/mL)	Fixed (test)*	117567.4	1.01	0.99 – 1.03
	Free (reference)**	116640.4		

*Fixed is the test treatment: 320/5 valsartan/amlodipine final market image (FMI) combination tablet. **Free is the reference treatment: 320/5 free combination of 160 mg valsartan CSF capsules and 5 mg amlodipine CSF capsule.

COMMENT:
The 320/5 mg of valsartan / amlodipine combination tablet is bioequivalent to the free combination of 320 mg valsartan and 5 mg amlodipine capsules coadministered together, with respect to both AUC and Cmax.

4.2.6 A pharmacokinetic interaction trial between valsartan and amlodipine following single doses in healthy subjects.

Study No. [VAA489A37]
Name of finished product: Diovan® and amlodipine
Name of active ingredient (s): valsartan and amlodipine
Investigators/Centers: [redacted]

Objective:
To determine whether a pharmacokinetic interaction exists between amlodipine and valsartan following single doses of 160 mg valsartan capsule, and 5 mg amlodipine tablet, alone and in combination, in healthy subjects.

Design:
This was a single-center, randomized, open-label, three-way crossover single dose trial in healthy subjects with a two week washout period between doses.

	Screening, Visit 1	Dose 1, Visit 2	Dose 2, Visit 3	Dose 3, Visit 4	Close-out, Visit 5	Total included in analysis
Number of subjects:	25	20	15	14	14	12

Criteria for inclusion (trial population): Healthy male subjects, aged 15-45 years, weight (kg) ± 15% of desirable values for height and body frame (1983 Metropolitan Height and Weight Tables), health screen without prohibitive findings, ability and willingness to cooperate, written informed consent obtained.

Reference and test products, dose and mode of administration, batch and formulation:

Drug	Strength	Batch No.	Formulation No.
Valsartan	Capsules, 160 mg	E-15177, E-15333	H-3577
Amlodipine	Tablets, 5 mg	E-15439, E-15463	H-3812, H-3825

Treatments:
Treatment A – one 160 mg valsartan capsule administered orally as a single dose;
Treatment B – one 5 mg amlodipine tablet administered orally as a single dose;
Treatment C – one 160 mg capsule of valsartan and one 5 mg tablet of amlodipine administered orally together as a single dose, free combination.

Mode of administration: p.o. doses together with 240 ml of water following an overnight fast
Duration of treatment: 10 weeks

Criteria for evaluation: Plasma concentration-time profiles were evaluated to determine the following pharmacokinetic parameters: AUC (0-t), the area under the curve from zero to the last sampling point; AUC (0-8), the area under the curve from zero to time infinity; Cmax, the highest observed plasma concentration for each dose; and Tmax, the time after each dose at

which the highest observed plasma concentrated was reported. The parameters determined for valsartan and amlodipine administered as a free combination were compared to parameters determined for each drug administered alone. It was not the intent of this study to evaluate these results according to standard bioequivalency methodology, but rather to use these measures as a guide to interpretation of a pharmacokinetic interaction.

Statistical methods:

Primary analyses were based on the 90% confidence intervals for the log-transformed AUC and Cmax data for the effect of amlodipine on valsartan pharmacokinetic parameters (Treatments A and C) and the effect of valsartan on amlodipine pharmacokinetic parameters (Treatments B and C). AUC and Cmax pharmacokinetic parameters were analyzed using an analysis of variance model containing the factors sequence, subject within sequence, treatment, and period. A preliminary test for carryover was also performed. For comparison of AUC and Cmax log-transformed parameters for each drug, 90% confidence limits for the difference between least squares means on the log-scale were anti-logged to provide 90% confidence limits for the ratio of the two least squares means on the untransformed scale. Supplementary statistical analyses were reported.

Results:

Pharmacokinetics:

The confidence intervals for the log(Cmax) values of valsartan (0.69 to 1.04) exceeded the standard bioequivalency criteria (following table).

Table 38 Summary table for valsartan (t=48) and amlodipine (t=168) pharmacokinetic parameters

Treatment	AUC (0-t) (ng hr/ml)	AUC (0-∞) (ng hr/ml)	Cmax (ng hr/ml)
valsartan only (Treatment A)	17750 ± 8719 49% CV (N=12)	18063 ± 9775 54% CV (N=9)	2307 ± 1024 44% CV (N=12)
valsartan with amlodipine (Treatment C)	17993 ± 12228 68% CV (N=12)	19614 ± 14084 72% CV (N=9)	2269 ± 1571 69% CV (N=12)
90% Confidence Intervals for log-transformed values for ratio (C vs. A)	(0.81, 1.07)	(0.85, 1.17)	(0.69, 1.04)
amlodipine only (Treatment B)	189 ± 43.2 23% CV (N=12)	213 ± 54.4 26% CV (N=12)	3.37 ± 0.94 28% CV (N=12)
amlodipine with valsartan (Treatment C)	192 ± 43.0 22% CV	226 ± 79.8 35% CV	3.54 ± 0.65 19% CV
	(N=12)	(N=12)	(N=12)
90% Confidence Intervals for log-transformed values for ratio (C vs. B)	(0.96, 1.08)	(0.96, 1.14)	(0.98, 1.16)

COMMENTS

1. According to the Guidance for Industry "In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Recommendations for Dosing and Labeling" : For both a substrate … and interacting drug … the maximum planned or approved dose and shortest dosing interval of the interacting drug (as inhibitors or inducers) should be used. **Neither valsartan nor amlodipine highest recommended doses were used in this DDI study.**
2. Since valsartan is a titratable drug for clinical use with wide therapeutic range, this observed difference is not clinically significant.

4.2.7 A randomized, open-label, single-dose, two-period crossover study in healthy subjects to evaluate the effect of food on the bioavailability of valsartan/amlodipine 160/10 mg fixed combination Final Market Image (FMI) tablet

Name of finished product: VAA489
Name of active ingredient: valsartan/amlodipine combination
Investigator(s): ————————————
USA Study center(s): ————————————
First subject dosed: 15-Nov-05 Last patient completed: 09-Dec-2005
Phase of development: III

Objective:
To evaluate the effect of food on the bioavailability of valsartan/amlodipine 160/10 mg fixed combination FMI tablet.

Study Design:
This was a randomized, single-dose, open-label, two period crossover study in healthy volunteers using valsartan/amlodipine (160/10 mg) fixed combination FMI tablet.
Each subject participated in a screening period (Day -21 to -2), a baseline evaluation in each treatment period (Day -1), two treatment periods with at least 14-day interval/washout between each period, and an end-of-study evaluation. Eligible subjects were randomized to one of two treatment sequences, with 18 subjects in each of the two sequences.
Following an overnight fast of at least 10 hours, subjects randomized to receive the treatment under fed conditions the standard FDA breakfast is provided, and subjects should eat it within 30 minutes. The study drug should be administered within 5 minutes after completion of the meal. The breakfast meal composition will consist of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz (100 g) of hash brown potatoes, 8 fl oz (about 240 ml) of whole milk. In all treatment periods, subjects checked in to the study center on Day – 1, at least 12 hours prior to dose administration. Safety assessments were performed and inclusion/exclusion criteria were reviewed to confirm subject eligibility. Subjects remained at the study center until 48 hours post dose for pharmacokinetic and safety assessments. Subjects were then discharged, but returned to the study center on an ambulatory basis on Days 3, 4, 5, 6 and 7 for additional pharmacokinetic assessments. The interval/washout period between each dose was at least 14 days. An end-of-study evaluation was performed on the last day of the last treatment period, after collection of the final PK blood sample.

Number of patients (planned and analyzed): 36 healthy male and/or female healthy volunteers

Test product, dose and mode of administration, batch number:
VAA489 combination FMI tablet 160/10 mg, oral administration, Batch: H061KA

Duration of treatment: Two periods lasting 168 hours post dose for pharmacokinetic and safety assessments with a 14 day washout period between the two single dose treatments.

Reference therapy, dose and mode of administration, batch number: None

Pharmacokinetic assessments:
All blood samples were taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. For each of the following time points, 4 mL blood sample was drawn pre-dose, and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48,72, 96, 144 and 168 hours post dose.

Bioanalytics:
Valsartan and amlodipine in plasma was determined simultaneously using a validated LC-MS/MS method. The lower limit of quantitation (LLOQ) of valsartan was 5 ng/mL and the LLOQ of amlodipine was 0.075 ng/mL using 300 µL plasma.
The following time points were analyzed for valsartan and amlodipine.
For valsartan: predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post dose.
For amlodipine: predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 144 and 168 hours post dose.
The data from all completed subjects were included in the pharmacokinetic (PK) data analysis. Concentrations were given in mass per volume units. Missing values or those below the limit of quantification were indicated in the data listings and treated as zero in data presentations and calculations. Pharmacokinetic parameters, expressed as mean, SD, and CV, were determined using non-compartmental method(s) with ———————————
The plasma concentration versus time profiles of valsartan and amlodipine were presented graphically on linear coordinates for each subject and mean profiles were presented for each treatment.

Statistical methods:
Valsartan and amlodipine PK parameters (AUCs and Cmax) were logarithmically transformed and analyzed using a linear mixed effects model, with fixed effects for sequence, treatment, period and a random effect for subject nested within sequence. The resultant 90% confidence intervals of the treatment mean ratios (fed/fasted) were used to evaluate the effect of food.

Results
Demographic characteristics
The 37 subjects enrolled had a mean age of 34.0 (range: 18-45 years), a mean weight of 76.3 (range: 51.4 – 105.4 kg). All subjects were healthy volunteers.

		Total
Number of subjects randomized		37
Age (years)	Mean	34.0
	SD	8.2
	Median	35
	Range	18-45
Gender – n (%)	Male	30 (81.1%)
	Female	7 (18.9%)
Race – n (%)	Black	25 (67.6%)
	Caucasian	12(32.4%)
Weight (kg)	Mean	76.3
	SD	11.30
	Median	74.1
	Range	51.4–105.4

Bioanalytical results: Assay validation for Valsartan and amlodipine is shown in the Table below.
Chromatograms were shown.

Table 39: Assay Characteristics for Valsartan

Parameter	Measure	Reviewer Comment
Linearity	5ng/mL to 10mcg/mL	Satisfactory
Precision (CV %)	≤ 10.2%	Satisfactory
Accuracy Between day	between -3.3% and 2.8%	Satisfactory
LLOQ	5 ng/mL	Satisfactory
Specificity		Satisfactory

Table 40: Assay Characteristics for Amlodipine

Parameter	Measure	Reviewer Comment
Linearity	0.075ng/mL to 15ng/mL	Satisfactory
Precision (CV %)	≤ 8.3%	Satisfactory
Accuracy Between day	between -1.6% and 1.7%	Satisfactory
LLOQ	0.075ng/mL	Satisfactory
Specificity		Satisfactory

Pharmacokinetic results: Pharmacokinetics of valsartan and amlodipine are summarized in the following tables.

Table 41. Mean (SD) pharmacokinetic parameters of valsartan

	Valsartan (arithmetic mean ± SD (CV%))		
PK parameter	Fed (test)	Fasting (reference)	Ratio of Geometric Means and 90%CI
AUC0-t (ng.hr/ml)	22943 ± 10199 (44.5%)	24211 ± 10522 (43.5%)	0.94 [0.81 – 1.11]
AUC0-∞(ng.hr/ml)	23409 ± 10225 (43.7%)	24678 ± 10598 (42.9%)	0.94 [0.81 – 1.10]
Cmax (ng/ml)	3497 ± 1671 (47.8%)	4138 ± 1993 (48.2%)	0.86 [0.73-1.02]
Tmax (hr)*	4 (1-10)	2.5 (1-4)	-
$t_{1/2}$ (hr)	10.5 ± 6.8 (65%)	10.2 ± 6.4 (63%)	-

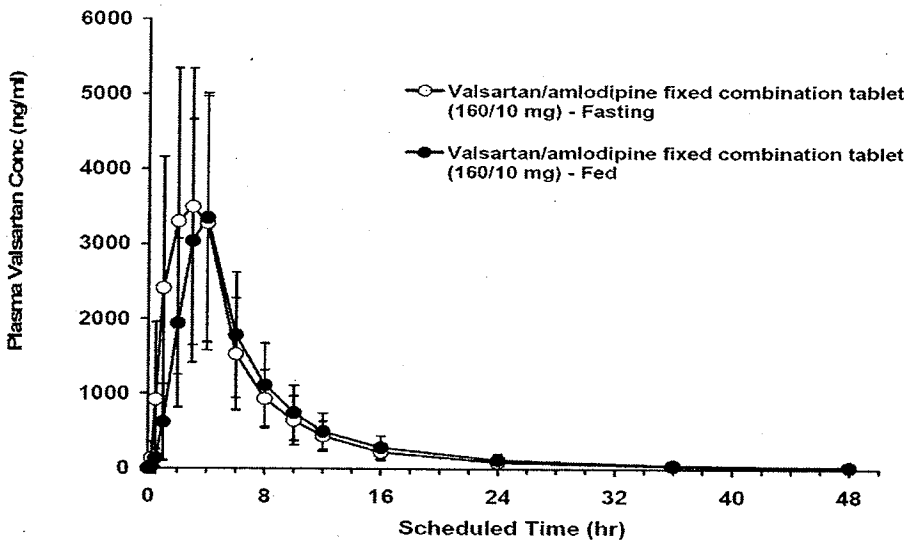


Figure 7. Mean (SD) of plasma concentration-time profiles of valsartan

Table 42. Mean (SD) pharmacokinetic parameters of amlodipine

	Amlodipine (arithmetic mean ± SD (CV%))		
PK parameter	Fed (test)	Fasting (reference)	Ratio of Geometric Means and 90%CI
AUC0-t (ng.hr/ml)	243 ± 79 (27%)	223 ± 85 (38%)	1.09 [1.05 – 1.13]
AUC0-∞ (ng.hr/ml)	268 ± 79 (33%)	248 ± 97 (39%)	1.09 [1.05 – 1.13]
Cmax (ng/ml)	4.8 ± 1.3 (27%)	4.6 ± 1.3 (27%)	1.03 [0.97 – 1.09]
Tmax (hr)*	8 (6-24)	8 (6-12)	-
$t_{1/2}$ (hr)	45.4 ± 9.2 (20%)	46.3 ± 11.2 (24%)	-

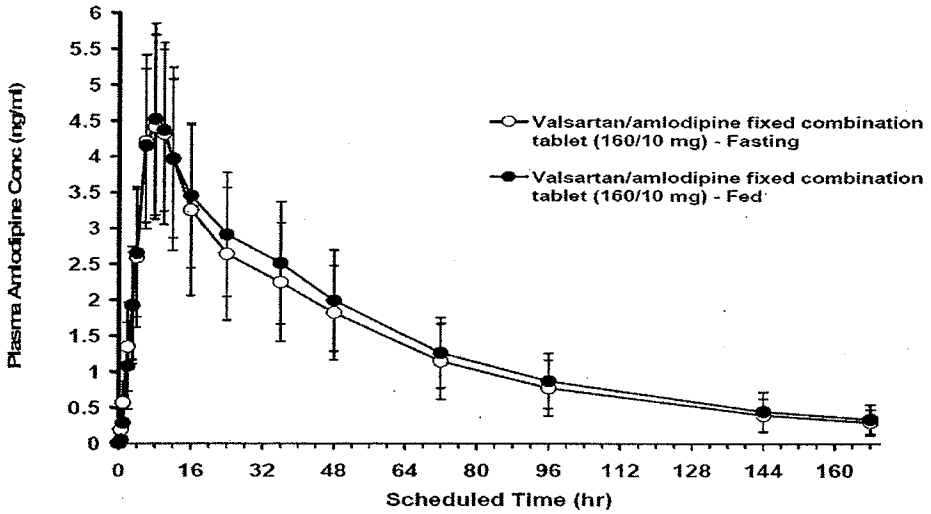


Figure 8. Mean (SD) of plasma concentration-time profiles of amlodipine

Table 43. Summary results of valsartan PK parameters

Parameter	Treatment	Geometric mean	Ratio of geometric means Fed/Fasting	90% CI for ratio
C_{max} (ng/mL)	Fed (test)	3162.8	0.86	0.73 – 1.02
	Fasting (reference)	3674.6		
AUC0-$_t$ (h*ng/mL)	Fed (test)	20601.1	0.94	0.81 – 1.11
	Fasting (reference)	21822.6		
$AUC_{0-\infty}$ (h*ng/mL)	Fed (test)	20941.7	0.94	0.81 – 1.10
	Fasting (reference)	22283.5		

Table 44. Summary results of amlodipine PK parameters

Parameter	Treatment	Geometric mean	Ratio of geometric means Fed/Fasting	90% CI for ratio
C_{max} (ng/mL)	Fed (test)	4.6	1.03	0.97 – 1.09
	Fasting (reference)	4.5		
AUC0-$_t$ (h*ng/mL)	Fed (test)	229.2	1.09	1.05 – 1.13
	Fasting (reference)	211.2		
$AUC_{0-\infty}$ (h*ng/mL)	Fed (test)	249.5	1.09	1.05 – 1.13
	Fasting (reference)	229.3		

REVIEWER COMMENTS

1. The highest dosing strengths for the combination of valsartan/amlodipine (320/5 and 320/10 mg doses) are bi-layer tablets containing Diovan and amlodipine layers over each other. The composition of these layers is close to the marketed formulations,

thus, a food effect study is not required. Therefore, the FDA recommended to conduct a food effect study with highest dose (160/10 mg) combination of : ——————— tablets ——————— 160/5 and 160/10 mg) and the design of this study is acceptable.

2. Following a single dose oral administration of 160/10 mg valsartan/amlodipine fixed combination tablet, the AUC values were similar in the fed and fasting conditions and the mean Cmax values of valsartan decreased by 16% in fed compared to fasting condition. The Cmax and AUC of amlodipine were similar between fed and fasting conditions.
3. Valsartan/amlodipine fixed dose combination tablet (Exforge) can be administered without regards to meals.

4.3 Biopharmaceutics

4.3.1 Formulation development

Initial clinical trials to assess the feasibility of developing an Amlodipine besylate and Valsartan combination product used 40 mg and 160 mg Valsartan capsules and over-encapsulated commercial 2.5 mg and 5 mg Norvasc (Amlodipine besylate) tablets.

The monolayer film-coated tablet formulations were modified based on the commercial Diovan (valsartan) film-coated tablet formulation and then subsequently modified with a [redacted] The appropriate amount of Amlodipine besylate was added.

Bioavailability clinical studies (Study #2302 and 2311) were carried out using monolayer film-coated tablets in the following strengths: [redacted] 10/160mg and 5/320mg. The [redacted] and 10/160mg formulations became the basis of the [redacted] and 5/160mg formulations which are weight and dose proportional to each other.

A new formulation for 5/320mg and 10/320mg film-coated tablets was developed using a bilayer tablet approach. The composition of the commercial formulations is shown below.

Table 45. Formulations of commercial drug product

Ingredient	5/160 mg	10/160 mg	5/320 mg	10/320 mg
Component (mg)				
Valsartan				
Amlodipine besylate				
Microcrystalline cellulose				
Crospovidone				
Colloidal silicon dioxide				
Magnesium stearate				
Sodium starch glycolate				
Iron oxide yellow				
Tablet core weight (mg)				
Coating weight (mg)				
Total tablet weight				

[redacted] corresponds to 5 mg of Amlodipine free base
[3] corresponds to 10 mg of Amlodipine free base
[4] removed during processing

The formulations of amlodipine and valsartan used in the pivotal placebo-controlled clinical studies 2201 and 2307 were exactly the same as the formulations of these drugs used for the definitive bioequivalence studies.

Table 46. Composition of Valsartan capsule formulations

Dosage strength/ Formulation Number	[redacted]	[redacted]	160 mg 3748183.010
Component			
Valsartan	[redacted]	[redacted]	160.0

Microcrystalline cellulose/ Cellulose microcrystalline		
Crospovidone		
Magnesium stearate		
Capsule contents		
Capsule shell – pink size 1		
Total capsule weight		

For the purpose of blinding, amlodipine tablets (2.5 mg and 5 mg) in the pivotal clinical studies were overencapsulated with the addition of microcrystalline cellulose (Table 47).

Table 47. Composition of Amlodipine capsule (over-encapsulated tablet) formulations

Dosage strength/ Formulation Number	**2.5 mg 3767571.001**	**5 mg 3767589.001**
Component		
Amlodipine (Norvasc 2.5mg tablet USA purchased)		
Microcrystalline cellulose/ Cellulose microcrystalline		
Capsule contents		
Capsule shell – pink size 1		
Total capsule weight		

q.s. = quantity sufficient

A comparative dissolution was performed between the commercial Norvasc tablet 2.5mg and 5 mg and the amlodipine capsule (over-encapsulated tablet) was performed in the following conditions:

Medium: 0.01N HCl degassed

Apparatus: USP 1 (Basket)

Temperature: 37 C

Speed: 100 rpm

Volume: 500 ml

The overencapsulation of the amlodipine tablets did not change the dissolution properties of amlodipine (Figure 9 and Figure 10).

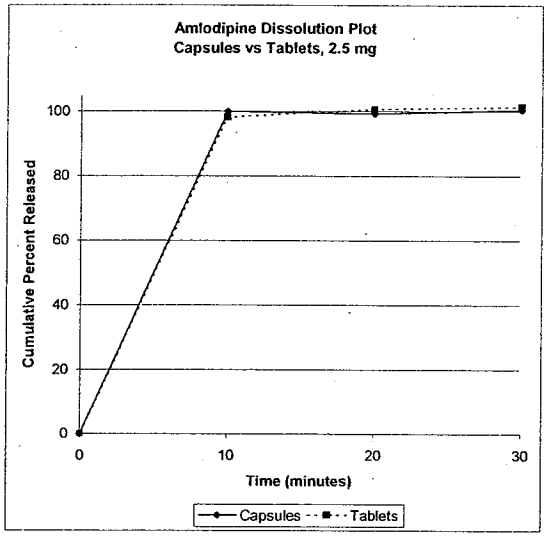


Figure 9. Dissolution profile commercial Norvasc 2.5mg tablet, batch #1QL138A vs amlodipine capsule (over-encapsulated tablet) 2.5mg, batch #07931.01, formulation KN3767571.001

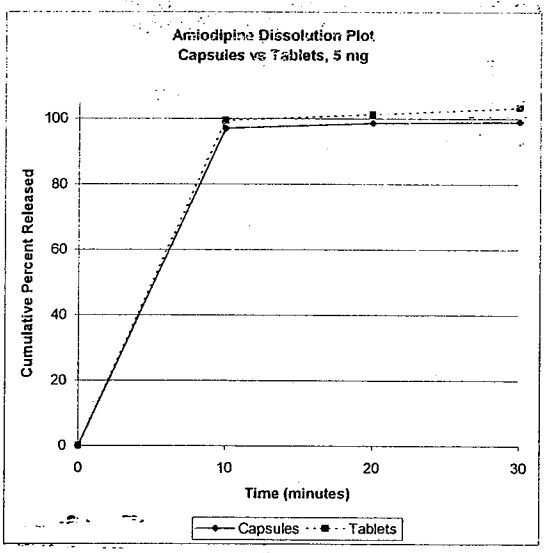


Figure 10. Dissolution profile commercial Norvasc 2 x 2.5mg tablet, batch #1QL138A vs amlodipine capsule (over-encapsulated tablet) 5mg, batch #07931.02, formulation KN3767589.001

4.3.2 Biowaivers

BE or BA studies have not been performed for the 5/80mg, 5/160mg and 10/320mg film coated amlodipine besylate and valsartan tablets and the sponsor has requested a biowaiver for these strengths.

Comparative dissolution profiles for both Amlodipine besylate and Valsartan were obtained on film-coated tablets in three different media, pH 6.8 (phosphate buffer), pH 4.5 (acetate buffer) and pH 1.0 (0.1 N HCl), 900 ml of dissolution media were used in Apparatus II (paddle) at 50 rpm. Dissolution profiles in the 3 media are provided comparing VAA489 5/80mg to 10/160mg, VAA489 2.5/80mg to 5/160mg and VAA489 5/320mg to 10/320mg. In addition, f2 similarity factors were calculated for each combination of tablets tested.

Bio-waiver request for the 80/5 mg valsartan/amlodipine dose

The bio-waiver for the 80/5 mg valsartan/amlodipine [redacted] is requested based on the following:

1. The composition of 80/5 mg valsartan/amlodipine [redacted] is proportional in its active and inactive ingredients to the 160/10 mg valsartan/amlodipine fixed combination FMI tablet, for which the bio-equivalence was established [CP-Study 2309]. In addition, the manufacturing process of the two products is identical.
2. Valsartan and amlodipine exhibit linear and dose proportional pharmacokinetics.
3. In vitro dissolution of valsartan and amlodipine is comparable in three pH media between the 80/5 mg and 160/10 mg fixed combination products.

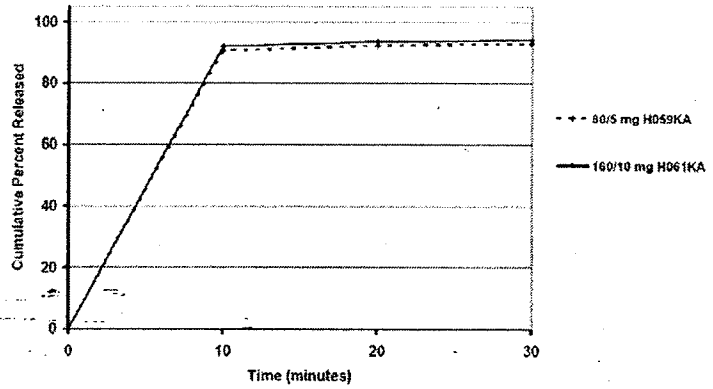


Figure 11. Dissolution profiles of valsartan: valsartan/amlodipine 80/5 mg fixed combination tablets [redacted], versus the 160/10 mg marketed tablets in the phosphate buffer pH 6.8 at 50 rpm (n = 12)

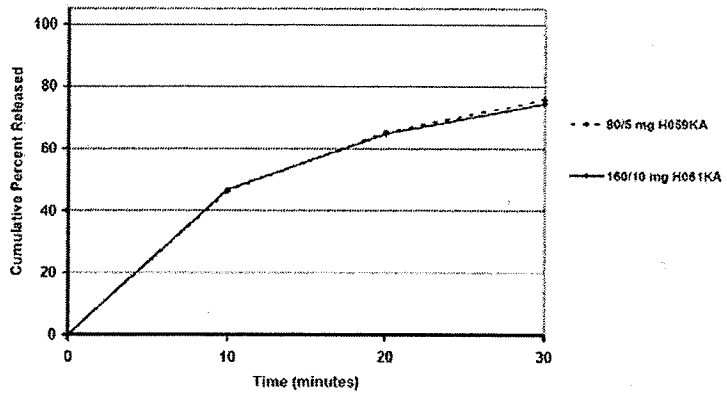


Figure 12. Dissolution profiles of valsartan: valsartan/amlodipine 80/5 mg fixed combination tablets —— versus the 160/10 mg marketed tablets in the acetate solution pH 4.5 at 50 rpm (n = 12)

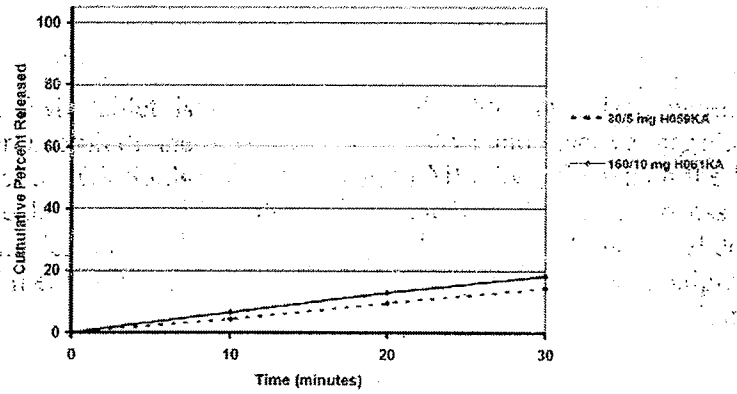


Figure 13. Dissolution profiles of valsartan: valsartan/amlodipine 80/5 mg fixed combination tablets —— versus the 160/10 mg marketed tablets in 0.1 N HCl pH 1.0 at 50 rpm (n = 12)

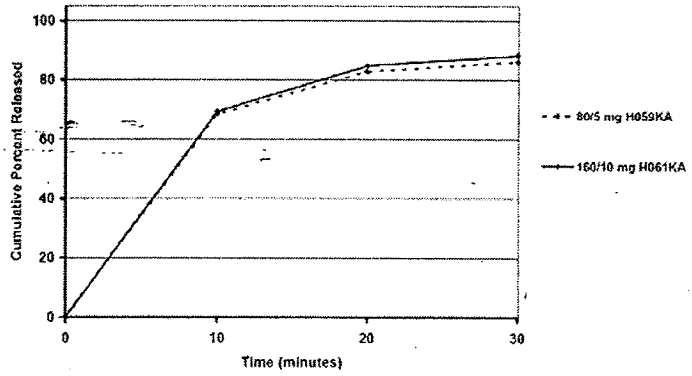


Figure 14. Dissolution profiles of amlodipine: valsartan/amlodipine 80/5 mg fixed combination tablets —— versus the 160/10 mg marketed tablets in the phosphate buffer pH 6.8 at 50 rpm (n = 12)

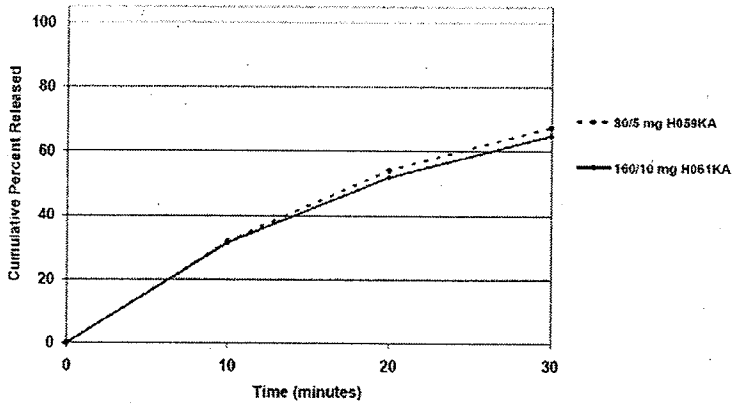


Figure 15. Dissolution profiles of amlodipine: valsartan/amlodipine 80/5 mg fixed combination tablets —— versus the 160/10 mg marketed tablets in the acetate solution pH 4.5 at 50 rpm (n = 12)

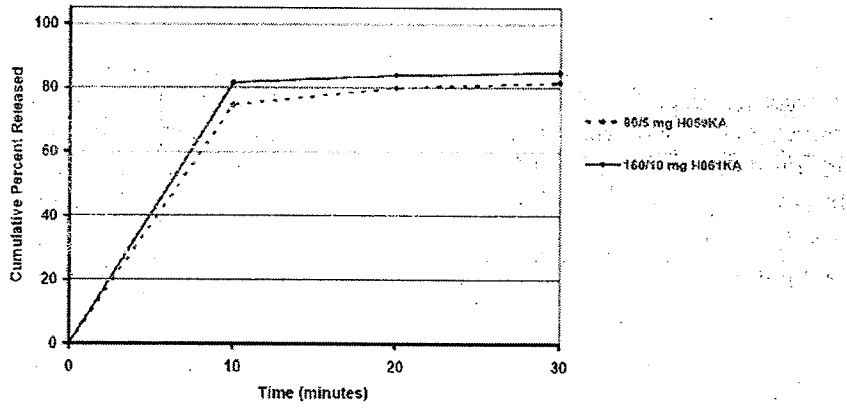


Figure 16. Dissolution profiles of amlodipine: valsartan/amlodipine 80/5 mg fixed combination tablets —— versus the 160/10 mg marketed tablets in 0.1 N HCl pH 1.0 at 50 rpm (n = 12)

Table 48 f2 similarity factors comparing dissolution profiles of 80/5 mg and 160/10 mg valsartan/amlodipine fixed combination tablets

Media	80/5 mg —— vs. 160/10 mg FMI tablet	
	Valsartan	Amlodipine
pH 6.8	89.8	84.7
pH 4.5	94.0	82.6
pH 1.0	73.2	64.9

COMMENT:
Mean cumulative % released versus time profiles of the 160/10 mg and 80/5 mg valsartan/amlodipine fixed combination tablets were similar in three pH media.

Bio-waiver request for the 160/5 mg valsartan/amlodipine dose

The bio-waiver for the 160/5 mg valsartan/amlodipine fixed combination FMI tablet is requested based on the following:

1. The composition of the 160/5 mg valsartan/amlodipine fixed combination FMI tablet is proportional in its active and inactive ingredients to the 80/2.5 mg valsartan/amlodipine fixed combination ——— for which the bio-equivalence was established [CP Study 2303]. The manufacturing process of the two products is identical.
2. Valsartan and amlodipine exhibit linear and dose proportional pharmacokinetics.
3. In vitro dissolution of valsartan and amlodipine is similar in three pH media between the 160/5 mg and 80/2.5 mg fixed combination products.

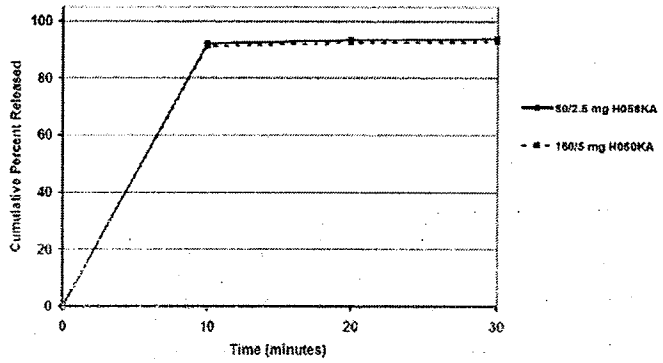


Figure 17. Dissolution profiles of valsartan: valsartan/amlodipine 160/5 mg fixed combination tablets ——— versus the 80/2.5 mg ——— in the phosphate buffer pH 6.8 at 50 rpm (n = 12)

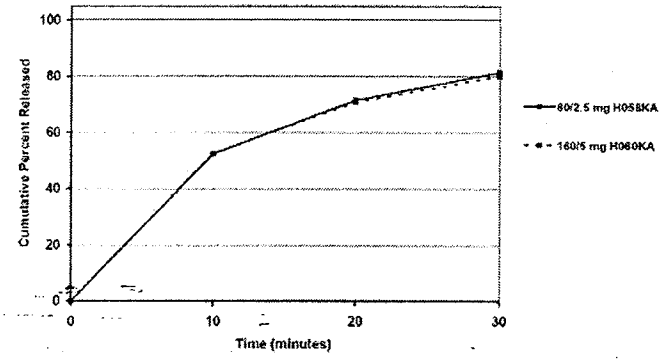


Figure 18. Dissolution profiles of valsartan: valsartan/amlodipine 160/5 mg fixed combination tablets——— versus the 80/2.5 mg ——— in the acetate solution pH 4.5 at 50 rpm (n = 12)

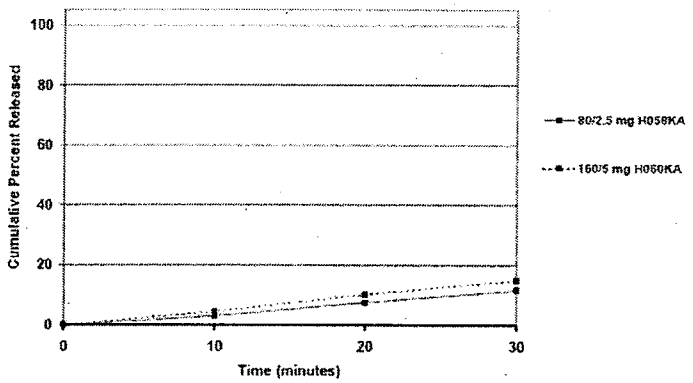


Figure 19. Dissolution profiles of valsartan: valsartan/amlodipine 160/5 mg fixed combination tablets (FMI) versus the 80/2.5 mg ——— in 0.1 N HCl pH 1.0 at 50 rpm (n = 12)

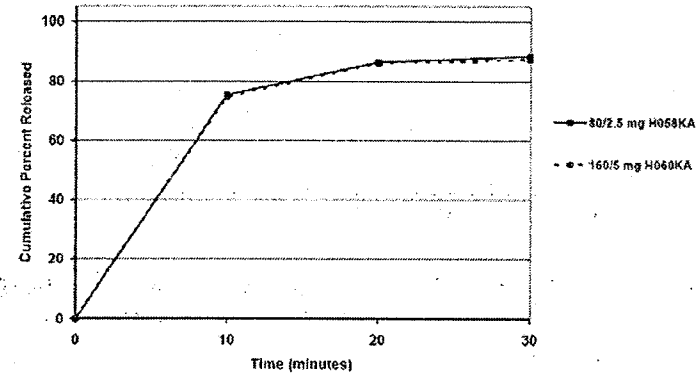


Figure 20. Dissolution profiles of amlodipine: valsartan/amlodipine 160/5 mg fixed combination tablets (FMI) versus the 80/2.5 mg ——— in the phosphate buffer pH 6.8 at 50 rpm (n = 12)

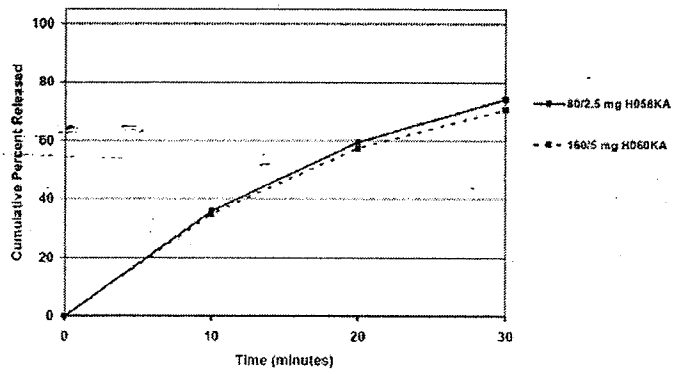


Figure 21. Dissolution profiles of amlodipine: valsartan/amlodipine 160/5 mg fixed combination tablets (FMI) versus the 80/2.5 mg ——— in the acetate solution pH 4.5 at 50 rpm (n = 12)

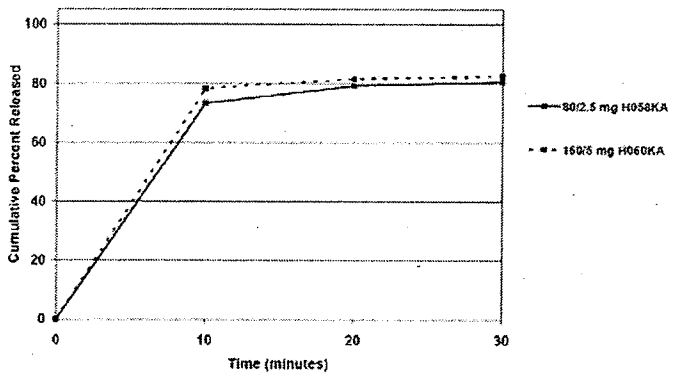


Figure 22. Dissolution profiles of amlodipine: valsartan/amlodipine 160/5 mg fixed combination tablets (FMI) versus the 80/2.5 mg [redacted] in 0.1 N HCl pH 1.0 at 50 rpm (n = 12)

Table 49 f2 similarity factors comparing dissolution profiles of 160/5 mg and 80/2.5 mg valsartan/amlodipine fixed combination tablets

Media	160/5 mg FMI tablet vs. 80/2.5 mg [redacted]	
	Valsartan	Amlodipine
pH 6.8	93.2	94.9
pH 4.5	93.4	78.8
pH 1.0	77.6	72.5

COMMENT:
Mean cumulative % released versus time profiles of the 80/2.5 mg and 160/5 mg valsartan/amlodipine fixed combination tablets were similar in three pH media.

Bio-waiver request for the 320/10 mg valsartan/amlodipine dose
The bio-waiver for the 320/10 mg valsartan/amlodipine fixed combination FMI tablet is requested based on the following:

1. The 320/10 mg valsartan/amlodipine formulation is a bi-layer tablet and its manufacturing process is identical to that of the 320/5 mg fixed combination bi-layer tablet, for which the bioequivalence was established [CP-Study 2310].
2. Composition of 320 mg valsartan layer of the 320/10 mg fixed combination tablet is the same as that of the 320/5 mg fixed combination tablet
3. The composition of the 320 mg valsartan layer is identical to the approved commercial Diovan 320 mg tablet.
4. Composition of the 10 mg amlodipine layer of the 320/10 mg fixed combination tablet is [redacted]

5. Composition and process changes do not affect the bioavailability of amlodipine as evidenced by the results from the bioavailability study [CP Study 2311]. In this study, comparable amlodipine bioavailability was shown with two prototype 320/5 mg tablets, whose composition and manufacturing processes were significantly different.
6. The time to reach maximum plasma concentration (Tmax) of amlodipine after an oral administration of an immediate release amlodipine besylate tablet is around 10 hrs, which suggest that minor changes in the dissolution properties of immediate-release amlodipine tablets will not influence the oral bioavailability of amlodipine.
7. Valsartan and amlodipine exhibit linear and dose proportional pharmacokinetics
8. In vitro dissolution of valsartan and amlodipine is similar in three pH media between the 320/10 mg and 320/5 mg fixed combination products.

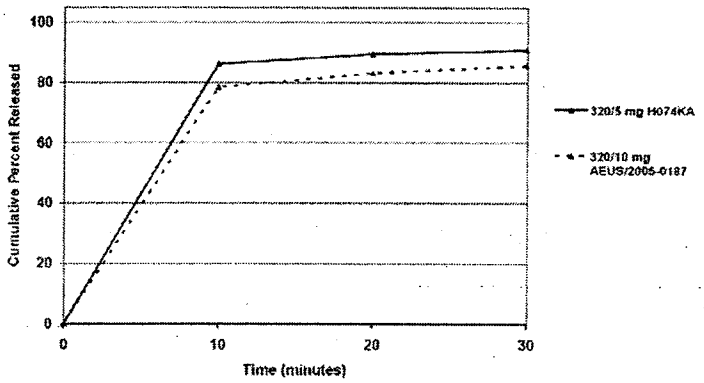


Figure 23. Dissolution profiles of valsartan: valsartan/amlodipine 320/10 mg fixed combination tablets (FMI) versus the 320/5 mg fixed combination FMI tablets in the phosphate buffer pH 6.8 at 50 rpm (n = 12)

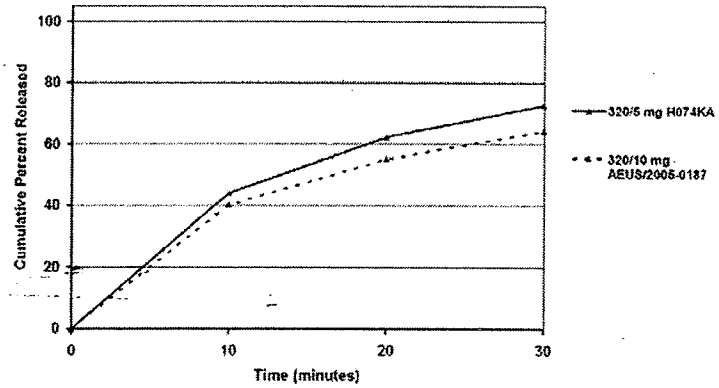


Figure 24. Dissolution profiles of valsartan: valsartan/amlodipine 320/10 mg fixed combination tablets (FMI) versus the 320/5 mg fixed combination FMI tablets in the acetate solution pH 4.5 at 50 rpm (n = 12)

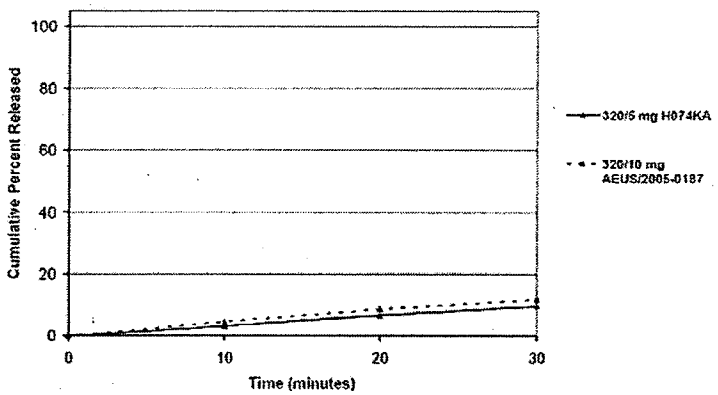


Figure 25. Dissolution profiles of valsartan: valsartan/amlodipine 320/10 mg fixed combination tablets (FMI) versus the 320/5 mg fixed combination FMI tablets in 0.1 N HCl pH 1.0 at 50 rpm (n = 12)

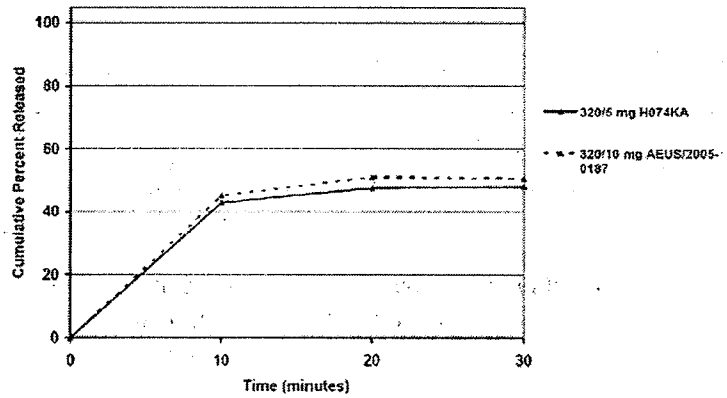


Figure 26. Dissolution profiles of amlodipine: valsartan/amlodipine 320/10 mg fixed combination tablets (FMI) versus the 320/5 mg fixed combination FMI tablets in the phosphate buffer pH 6.8 at 50 rpm (n = 12)

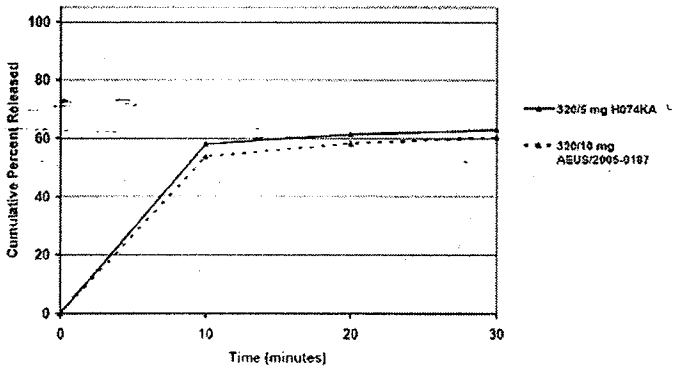


Figure 27. Dissolution profiles of amlodipine: valsartan/amlodipine 320/10 mg fixed combination tablets (FMI) versus the 320/5 mg fixed combination FMI tablets in the acetate solution pH 4.5 at 50 rpm (n = 12)

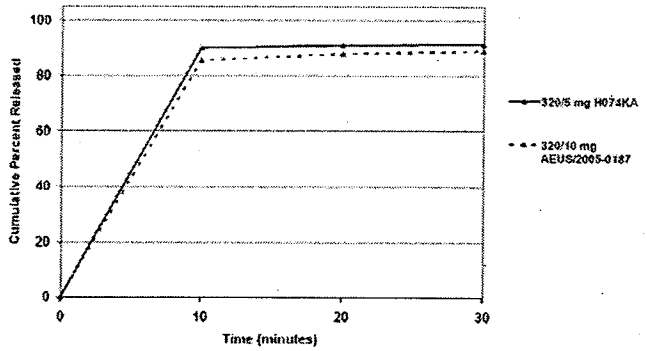


Figure 28. Dissolution profiles of amlodipine: valsartan/amlodipine 320/10 mg fixed combination tablets (FMI) versus the 320/5 mg fixed combination FMI tablets in 0.1 N HCl pH 1.0 at 50 rpm (n = 12)

Table 50. f2 similarity factors comparing dissolution profiles of 320/10 mg and 320/5 mg valsartan/amlodipine fixed combination tablets

Media	320/10 mg FMI tablet vs. 320/5 mg FMI tablet	
	Valsartan	Amlodipine
pH 6.8	59.2	76.5
pH 4.5	58.4	72.4
pH 1.0	83.4	72.1

COMMENT:
Mean cumulative % released versus time profiles of the 320/5 mg and 320/10 mg valsartan/amlodipine fixed combination tablets were similar in three pH media.

CONCLUSION:
The dissolution profiles of VAA489 film coated tablets were similar according to the f2 results (values between 58.4 and 94.0 for Valsartan and between 64.9 and 94.9 for Amlodipine). Based on these data a biowaiver for the tablets 5/80mg, 5/160mg and 10/320mg is granted.

4.3.3 Dissolution Method and Specifications

The sponsor proposed the following dissolution conditions and specifications:

Apparatus:	USPII Paddle
Speed of rotation	65 ± 2 rpm
Medium	Phosphate buffer pH 6.8 with 0.1 % Tween 80
Volume of test medium	1000 ml
Temperature	37 ± 0.5°C
Valsartan Q = ———	
Amlodipine, Q= ———	

The dissolution test results were not submitted for review.
At the teleconference with the sponsor (held on 9/06/2006), the Agency requested to submit the actual dissolution data for the method used. The justification for the use of a phosphate buffer medium with pH 6.8 and 0.1% Tween 80 at a rotation speed of 65 rpm was requested. The sponsor submitted (9/22/2006) the response to the FDA request.

1. The sponsor reported that the amlodipine solubility is not significantly different from pH 1 to 6.8, that was the justification of the use of pH 6.8 media for both drugs.

There were no additional data submitted to prove this claim, however, the information submitted for the biowaivers had amlodipine dissolution profiles at pH from 1.0, 4.5, and 6.8 (Figure 14, Figure 15, Figure 16, Figure 20, Figure 21, Figure 22, Figure 26, Figure 27, Figure 28). The solubility of amlodipine showed a dependency on the pH of the media. For example, the release of amlodipine at 30 minutes from the valsartan/amlodipine tablet of 320/10 mg was —— pH 6.8), — (pH 4.5) and — (pH 1).

2. The sponsor claimed that the addition of 0.1% Tween 80 to the dissolution media decreases the adsorption of amlodipine to glass and metal surfaces during the dissolution process and therefore, the variability of the method is lower with Tween.

The raw data show that the differences in variability for amlodipine preparations were very minor (Table 51).

Table 51. Standard Preparations of Amlodipine

Conditions	pH 6.8 + Tween day 1	pH 6.8 no Tween day 1
Standard Accuracy, range %	100.1-105.1	98.7-102.7

Moreover, when Tween was used, the variabilities of the tablet dissolution were larger than without Tween (Table 52).

Table 52. The 320/10 mg tablets dissolution data with and without Tween 80

pH 6.8 phosphate buffer without tween 80

pH 6.8 phosphate buffer with 0.1% tween80

pH 6.8 phosphate buffer without tween 80

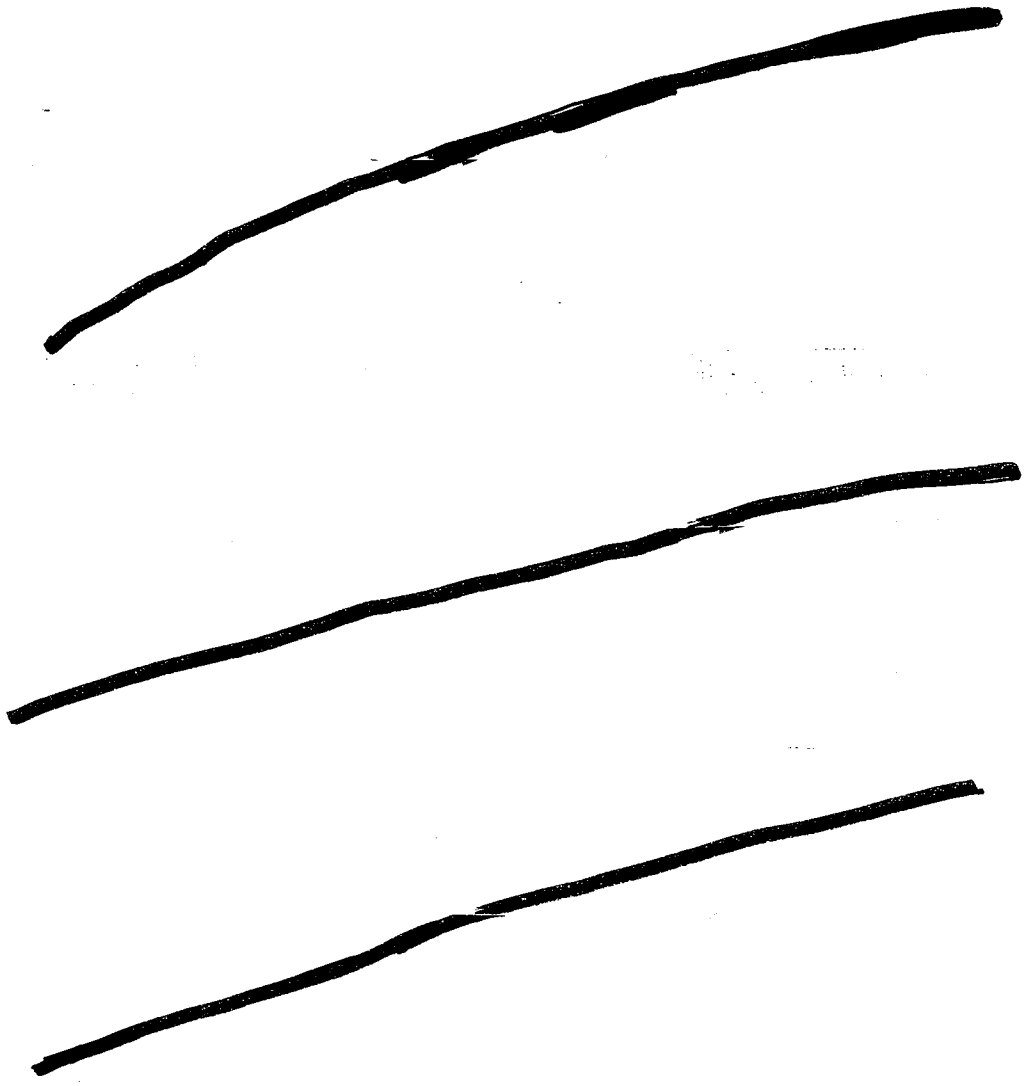
pH 6.8 phosphate buffer with 0.1% tween80

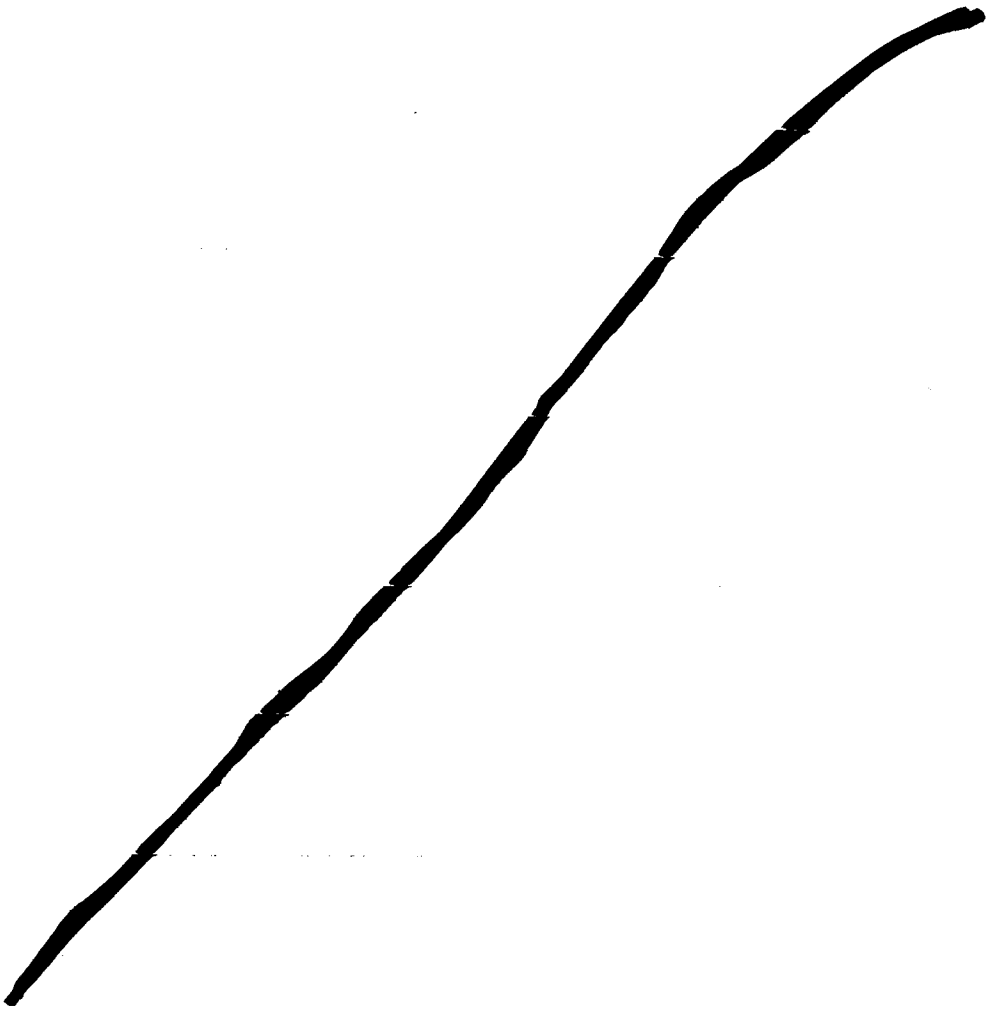
Therefore, there is no needed to use Tween for the dissolution medium.

3. The sponsor proposed to increase the dissolution rate of amlodipine by the use of 65 rpm rotation speed.

The three rotation speeds are compared in (Table 54 and Table 55). The dissolution rate of amlodipine at 65 rpm speed was higher than at 50 rpm. The sponsor did not provide the comparison of different rotation speeds with and without Tween 80. When the 65 rpm rotation speed was used, the variability of the method was very high.

Table 54. The 320/10 mg tablet, batch AEUS/2005-0186, paddle method, pH 6.8 phosphate buffer containing 0.1% Tween 80.





4. The specification of Q=—— for amlodipine is not acceptable since the complete dissolution is seen in the proposed medium.

CONCLUSION:
The Agency recommends the following dissolution specifications and methodology:

Valsartan

Apparatus:	USP II (paddle)
Medium:	0.067 M phosphate buffer, pH 6.8, 37°C
Dissolution Volume	900 ml of
Rotation Speed:	50 rpm
Specifications:	Q = ————

Amlodipine:

Apparatus	USP II (paddle)
Medium	0.1N HCL, pH 1.0, 37°C
Dissolution Volume	900 ml
Rotation Speed (rpm)	50 rpm
Specification (Q)	Q= ————

These dissolution specifications and methodology were obtained from the sponsor's dissolution data submitted in support of the waiver request.

4.4 Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-990	Brand Name	Exforge
OCPB Division (I, II, III)	DIV-1	Generic Name	combination of valsartan and amlodipine
Medical Division	CARDIORENAL	Drug Class	ARB/calcium channel blocker
OCPB Reviewer	ELENA MISHINA	Indication(s)	
OCPB Team Leader	P. Marroum	Dosage Form	Tablet: [redacted] 160/5 mg; 160/10 mg; 320/5 mg; and 320/10 mg
		Dosing Regimen	Starting from [redacted] QD up to 320/10 mg QD
Date of Submission	February 22, 2006	Route of Administration	oral
Estimated Due Date of OCPB Review	October 22, 2006	Sponsor	Novartis Pharmaceuticals
PDUFA Due Date		Priority Classification	S
Division Due Date			

Clin. Pharm. and Biopharm. Information	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	7		
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting /non-fasting single dose:	X	1		
fasting /non-fasting multiple dose:				
Drug-drug interaction studies -	[redacted]	[redacted]		
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X	5		
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				
traditional design; single /multi dose:	X	5		
replicate design; single /multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS	X			
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Electrophysiololgy Study				
Pharmacodynamic studies				
Total Number of Studies Reviewed	7			

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-990, HFD-850(Lee), HFD-860 (Marroum, Mehta, Mishina), Biopharm (CDER)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elena Mishina
11/1/2006 04:15:23 PM
BIOPHARMACEUTICS

please check page 13, and 76-78

Patrick Marroum
11/3/2006 01:24:44 PM
BIOPHARMACEUTICS